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The Journal of Allergy

VOL. 8 JANUARY, 1937 NO. 2

Original Articles

DIFFERENT DETERMINANTS OF ANTIGENIC SPECIFICITY ON SINGLE MOLECULES*

SANFORD B. HOOKER, M.D.
BOSTON, MASS.

DURHAM'S early conception that the bacterial cell is a mosaic of different antigens has been amply confirmed by recent antigenic analyses not only of bacteria but of erythrocytes, egg whites, serums, etc. The idea was extended to apply to purified proteins by Wells and Osborne (1913) in their explanation of the cross reactions in gliadin and hordein antibody systems; further antigenic studies of related vegetable globulins and of ovomucoids led Wells to state: "The entire protein molecule is not involved in determining the specific character of the immunological reactions, but this is developed by certain groups or radicals of the protein molecule and a single protein may contain two or more such groups."

This multiple determinant hypothesis, however, as applied to single proteins has not been unopposed. The evidence excluding the presence of an antigenic contaminant has not always been satisfactory; Landsteiner and van der Scheer (1924) found "no conclusive evidence of the regular existence in a single immune serum of multiple antibodies which act specifically on various chemical groups of the antigenic proteins."

The solution of this problem is not only of interest but also of practical significance to the student of antigens. If two or more determinants exist on a single molecule and give rise to molecularly different antibodies, it would, if unrecognized, effectively confuse the analyst who should attempt to isolate such antigenic properties by any of the methods used in separating different kinds of molecules.

*From the Evans Memorial, Massachusetts Memorial Hospitals.

Presidential address before the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 2, 1936.

The multiple determinant hypothesis is not inherently improbable: relative to antigen antibody *unions* we have the analogy of the formation of simple chemical compounds that depend upon primary valence; e.g., different atomic groups of a given molecule are involved in different reactions as in the formation of acetylsalicylic acid by combining acetic anhydride with the OH group of the acid, whereas oil of wintergreen results from a combination of methyl alcohol with the COOH group. Another pertinent analogy is afforded by specific adsorption in which intermolecular forces other than primary valence are concerned; these forces are surely of great importance to the specificity of antigen antibody unions. One example involving simple substances of known composition depends merely upon the different spacing of the carbon atoms on the adsorbing surfaces: diamond adsorbs methylene blue but not succinic acid, whereas graphite behaves in the reverse manner. Marrack points out that specific adsorptive forces become progressively more important as the size of the molecules increases; in immunology we deal mostly with large molecules.

Moreover, among idiosyncratic responses to drugs, there are many examples of the individual, qualitative significance of submolecular groups. Sensitiveness to iodine is common; yet an individual reactive to iodoform may be affected only by the methyl group of the molecule. A striking illustration is afforded by the studies of Dawson and others on the different chemical bases of the allergic reactions of three different subjects to the dextro- and levorotatory forms of many cinchonal alkaloids.

Another probable instance of the qualitative diversity of effect of multiple groups is offered by the behavior of artificially compounded antigens: partly iodized horse serum evokes one kind of precipitin which reacts with iodized chicken serum and another which reacts with unmodified horse serum, i.e., the conjugated atom of iodine (with some atomic groups immediately surrounding it) conditions one kind of specificity, while other natural groupings are sufficiently unchanged so that some species specificity is retained. It was during a study of one of these synthetic antigens, gelatin-diazo-arsanilic acid, that my interest in this question of multiple determinants was first aroused. The formation of azoprotein dyes has been thought to be mediated through the amino acids, tyrosin and histidin. Gelatin is deficient in tyrosin but contains histidin; "complete" proteins contain both. It appeared possible that the peculiar quantitative behavior of anti-azogelatin as compared with anti-azo-egg-white might be explained by assuming that the former contained only the antibody or antihapten more specifically related to histidin-azo-arsanilic acid. Inhibitive reactions with purified haptens (diazonium compounds of arsanilic acid with phenol and iminazol—the respective cyclic nuclei of tyrosin and histidin) gave support to this assumption and were not open to the objection regarding

impurity of reagents which has been raised against previous work. Still, the serologic behavior of artificially conjugated prosthetic groups might be only a special case; so it was desirable to test the assumption in systems involving natural antigens.

For this purpose, crystallized ovalbumins from the hen and the duck were selected for many reasons, which, with the evidences of purity, I have detailed at tedious length elsewhere. Besides rabbits, I immunized hens and ducks with the expectation, later realized, that *horror autotoxicus* would allow the birds to respond with the production of antibody only to the heterologous *specific* component and not to the albumins' *common* or *group* component, should such exist. Briefly, the results supported the conception that the molecules of these proteins, rigorously tested for molecular homogeneity, possess different and individually specific as well as similar common antigenic determinants.

We do not assume that every natural antigen must produce more than one kind of antibody or that cross reactivity is always necessarily due to the presence of molecularly separate antibodies; a sufficiently complex antibody (Heidelberger and Kendall) could also produce cross reactions. There seems to be, at present, no good reason why each explanation may not sometimes be applicable, or necessary, depending upon the nature of the antigen injected and the individual animal's response to it. In the work of other investigators also I found some dormant evidence of the presence of different determinants in certain polysaccharides and compound proteins. The cross reactivity of *B. Friedländeri*, type B, with pneumococcus, type II, was a case in point. Even more convincing were the studies of Avery, Goebel, and Babers on the haptenic specificity of the β-glycosides of glucose and galactose in comparison with α- and β-glucosides. Here were shown clearly the coexisting specific influences that center about the configurations surrounding the fourth carbon atom of the carbohydrate ring *and* the *cis* or *trans* position of the substituents attached to the first carbon atom.

Other supportive evidence has been forthcoming: Landsteiner and van der Scheer (1932) studied the haptenic properties of related peptides and found the terminal group to be most influential, but the adjacent amino acid somewhat affected specificity. "Another alternative implying the action of several antibodies requires further investigation."

Likewise, Avery and Goebel found that in type I pneumococcal antiserum there seem to exist at least two antibodies, both or all of which are removable by the acetylated polysaccharide, but only one or a part combines with the (deacetylated) S I as ordinarily prepared. Some appear to doubt that it is the acetyl group which rounds out the complete (complex) hapten; but that *some* additional group is essential can hardly be disputed. Goebel, Avery, and Babers found that a pro-

nounced alteration of specificity resulted from coupling an acetyl group with the sixth carbon atom of the hexose portion of *p*-amino-phenol β-glucoside. Their intricate analysis of the specificity of the glycosidic disaccharide haptens, cellobiose, gentiobiose, lactose, and maltose revealed the determining influence of the molecule as a whole, of the configuration of the terminal hexose, and of the position of linkage of the two hexose units. Heidelberger and Kendall have recently covered the hydroxyl groups of S III with methyl groups and found that the methylated hapten could remove only a portion of the antibodies in homologous antiserum. They cited other evidence for a multiplicity of antibodies and considered "that on the S III molecule there is, in addition to the molecular grouping carrying hydroxyl groups, at least one other molecular grouping which is immunologically reactive and independently so."

In a study of the specific polysaccharidic hapten of *Bact. shigæ*, Meyer and Morgan found support for "the view that a chemically homogeneous bacterial polysaccharide hapten may contain two determinant groups of diverse specificity, and . . . may induce the formation of two antibodies, each of which is specifically related to the corresponding determinant or receptor group in the polysaccharide molecule." Similarly, Burnet concluded that "A Flexner dysentery bacillus extract is composed of immunologically similar but complex antigen molecules, and not of the mixture of antigens postulated according to the mosaic theory of bacterial antigenic structure."

The radical change in specific reactivity produced by hydrolysis of esterified *p*-aminobenzoic acid is a particularly clear revelation of the importance of small parts of single molecules.

Thus a score of different systems yield harmonious evidence for the production of multiple antibodies in response to a single antigen, and for the importance of small portions of single molecules as determinants of specificity.

Finally, Landsteiner and van der Scheer (1936) have returned to the problem and studied the cross reactions of immune serums to azoproteins; they clearly demonstrated that multiple antibodies may be evoked by an individual specific structure such as metanilic (*m*-amino-benzene-sulphonic) acid coupled with protein. But they state that this "is no proof of the existence of several substances or special groups in the immunizing antigen." The view that "the antibodies present in one immune serum are severally directed toward distinct groupings or components of the antigen . . . while possible in cases of natural antigens is not tenable in those under discussion. It appears that the specificity is determined by the structure of the metanilic acid as a whole. Clearly, there are not several specific groupings in the immunizing antigen, identical with groupings contained in the positively reacting heterologus antigens, to which the antibodies could be specifically related."

Thus we have agreement that a single antigen (or complex hapten) can give rise to qualitatively different antibodies, and this is the essentially important result. Concerning the existence of several different groupings on the antigenic molecule the disagreement need not be fundamental; I think it may depend on a slight difference in the point of view from which one forms a mental picture of the antigen antibody relationship. Landsteiner would not exclude the possibility of different groupings for he states: "The tendency for the production of multiple distinct antibodies might possibly be greater with larger molecules, and one may assume that there will be transitions to those cases in which sharply separated determinant groups exist in one molecule." This conception of a sharp separation—that is, the different groups being pictured at a considerable distance* from each other—could give rise to discrepant opinions. One could look upon metanilic acid, for example, as a single determinant; another might regard it as a single *complex* determinant containing a number of atomic groupings sufficiently varied in chemical nature and spatial relationships to allow the assumption that many different combinations, such as ABCD, ACD, B′CA, might be "subdeterminants" capable of evoking the corresponding antideterminants abcd (or abc, etc.), acd, b′ca.†

Indeed the unequivocal evidence for the importance of spatial configuration, afforded by the serologic differentiation of steric isomers, forces the assumption of multiple binding points. When we consider that the molecule of antibody globulin possesses one or more areas wherein the atomic groups or "fields of force" exist in very precise, mirror-image correspondence with homologous groups on the antigenic molecule, we must assume the existence of *at least three* such spatially adapted points in order to explain the specificity of *l*- and *d*-phenyl-

*The attractive potency of the various intermolecular combining forces diminishes very rapidly with increase in distance between the reactants. That of the strongest, primary valence (cf., the *marked* influence of acidic groups upon specificity), varies inversely as the square of the distance; some of the others, van der Waals forces and magnetic forces between dipoles, are very much weaker and vary inversely as the fourth power of the distance. If, as seems likely, some of these forces other than primary valence are involved in the antigen antibody reaction, then it becomes probable that the componert factors of a complex determinant must be in close proximity unless considerable distortion can take place. The deformability of proteic molecules in solution has not been thoroughly studied.

†B and B′ may be considered to represent identical atoms or small atomic groups which, however, occupy different positions with respect to their surrounding groups. Thus, a simple determinant group such as ABC would differ configurationally from AB′C, and this difference might readily be reflected in the corresponding antibodies as, for example, in the case of antiglucoside and antigalactoside.

The relative influence of single atoms upon serologic specificity has not been studied by precise quantitative methods. Halogenated proteins react most strongly, by the antigen dilution technic, with their homologous antiserums. This could possibly be ascribed to different changes in the protein other than the disubstitution in the tyrosin groups which appears to be the important alteration. But inhibition with the simple haptens—3.5 dihalogenated tyrosins—reveals the same differences; their inhibitive effect upon an immune serum for iodoprotein diminishes in the order I, Br, Cl. The outer shell of electrons, upon which ordinary chemical reactions depend, is identical in each of these atoms. Perhaps the quantitative difference in serologic activity results from slightly different distortions in the disubstituted molecules of tyrosin caused by some quality of the inner electronic shells or the nuclei of these halogens.

Another pertinent example, involving P, As, and Sb, whose outer electronic structures are the same, has been reported by Erlenmeyer and Berger. *P*-aminophosphanilic and -arsanilic acids were considered immunologically equivalent, but -stibanilic acid was different. It is significant that salts of phosphoric and arsenic acids are isomorphous, whereas those of stibinic acid are quite different.

acetic, or *l*-, *d*-, and *m*-tartaric acids. Were only two points postulated, then heterologous combination could be permitted merely by suitable orientation of either (antigen or antibody) molecule—both being rotationally mobile. Similar considerations apply when we think of the specificity of natural antigens. Carboxyl, hydroxyl, and amino groups are known to be importantly concerned in various specific serologic reactions, but different proteic molecules are more or less studded with these groups, and it is therefore inadmissible to assume that any such group *singly* (or perhaps even paired groups) can account for serologic specificity. Further indication of the existence of several distinct binding groups is shown by the superior specificity and inhibitive effect of amino or nitrotartranilic acids as compared with simple tartaric acids; this directly suggests that the antibodies involved act not upon the tartaric acid part of the molecule only but combine also with the aromatic nucleus. Likewise in the case of glucose and galactose, it was found that the simple sugars in the amounts used were not inhibitive; whereas the more complex glycosides inhibited strongly and specifically even though the only structural difference between them centers around the fourth carbon atom of the simple hexose portion of their molecules. Probably the relative dissociation constants must be considered in these cases.

If, then, multiple distinct binding groups or forces exist on molecules of antibody, it is reasonable to suppose that corresponding multiple groups or patterns of attractive forces exist on the homologous antigen or hapten; otherwise with what do the antibody groups combine? If the synthesis of antibody takes place under the orientative influence of the molecular structure of a pure antigen, then, if multiple antibodies result, it is reasonable to suppose that they were formed in correspondence with multiple determinants on the antigenic molecule. We may plausibly surmise that the most perfect (master key) antibody molecules are those that most accurately and completely reflect the dominant atoms and structures which determine antigenic specificity. It is likely that in many serums there are numerous grades of more and more imperfect and progressively more dissociable antibodies down to the sort that has the minimal number of combining groups, or an arrangement of groups with the least affinity, permissive of any recognizable association with antigen. The high dissociation constant of some simple haptens, with but one combining group, affords an analogy to this speculation.

SUMMARY

Molecularly homogeneous antigens can stimulate the formation of molecularly separate and qualitatively different antibodies. There is strong evidence that this should be ascribed to different submolecular components of the antigen.

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MUTUAL ABSORPTION TESTS WITH RELATED FOODS*

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IN THE field of inhalant sensitivity the work of Cooke, Stull, Hebald and Barnard,[1] Spain and Hopkins,[2] as well as others, has served to emphasize the essential identity of the antigen present in various related pollens. Common antigens in horse serum and horse dander have been shown by Tuft.[3] Coca and Grove[4] have described the same phenomena associated with cottonseed and kapok. As early as 1913 Wells and Osborne[5] in a study of antigenic relations of vegetable proteins showed that a guinea pig sensitive to either of certain proteins of wheat, rye, or barley could be shocked by the same proteins derived from the other two. Later, Vaughan[6] and Ellis[7] grouped various foods in a genetic classification and have emphasized the tendency for reactivity to take place according to this grouping.

The present paper is a report concerning cases of definite food sensitivity that we have encountered in the New York Hospital Allergy Clinic. In these cases, related foods have caused clinical sensitivity confirmed by skin testing and passive transfer. Using the in vitro neutralization method, we tried to show the presence of mutual excitants in these foods as related to these cases. The cases include sensitivity to certain grains, vegetables, fruits and fish.

The technic employed was as follows: A mixture of equal parts of atopen and a serum containing reagins for the atopen in question was made in a sterile test tube, shaken, incubated for one hour at 37° C. and placed in the refrigerator overnight. Controls of equal parts of serum and diluent were also shaken, incubated, and placed in the refrigerator. Passive transfer sites of 0.05 to 0.1 c.c. of each mixture were made on normal recipients (medical students) who had previously been tested and found to react negatively to the atopens used in the experiment and who had no history of personal or familial allergy. Sites were then tested forty-eight to seventy-two hours later. One site was always tested first with the atopen used in neutralization to confirm completeness of exhaustion. If the site continued to react, neutralization of it was continued in vivo. Sites were then tested with other atopens of the related group. To control specificity a nonrelated atopen, consisting of ragweed in the case of patients sensitive to this, was injected into the site showing neutralization. Where the serum used contained no

*From the Allergy Clinic of the New York Hospital and Cornell University Medical College, New York City.

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reagins for ragweed, a serum from another patient sensitive to ragweed was added to the incubated mixture. The ragweed solution used for testing contained 0.1 mg. of nitrogen per c.c. Nitrogen contents of other solutions used are indicated in the following tables.

The first case to be presented showed mutual absorption by celery, carrot, parsley and parsnip (Umbelliferae family).

CASE 1.—M. O., female, domestic, aged twenty-six years, has had asthmatic attacks for about two years. She sneezes and has itching of mouth and throat on eating raw carrots and celery. Urticaria and itching on palms of hands occur with scraping carrot and celery. Skin testing gave marked reactions to carrot, celery, parsnip and parsley, which were confirmed on passive transfer. (Table I.)

TABLE I

PATIENT M. O., SENSITIVE TO CARROT, CELERY, PARSLEY, AND PARSNIP

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Carrot	3+
		2	Celery	4+
		3	Parsley	2+
		4	Parsnip	2+
		5	Ragweed	3+
Carrot	0.32	6	Carrot	neg.
		7	Celery	neg.
		8	Parsley	neg.
		9	Parsnip	neg.
Celery	0.32	10	Carrot	neg.
		11	Celery	neg.
		12	Parsley	neg.
		13	Parsnip	neg.
Parsley	0.32	14	Carrot	neg.
		15	Celery	neg.
		16	Parsley	neg.
		17	Parsnip	neg.
Parsnip	0.32	18	Carrot	neg.
		19	Celery	neg.
		20	Parsley	neg.
		21	Parsnip	neg.
		22	Ragweed	3+

Experimental.—Serum from this patient incubated with diluent and injected into a normal recipient gave positive passive transfer reactions to carrot, celery, parsley and parsnip. When the serum was incubated with carrot extract, it no longer reacted to carrot, celery, parsley and parsnip. Absorption tests carried out with the other three members of the group likewise served to neutralize reactivity to the others. To control the specificity of the reaction, a serum from a ragweed sensitive patient was added to the serum-parsnip mixture which failed to show any reactivity to the other members of the group. A strong reaction was obtained to ragweed.

The second case shows mutual absorption by apple, quince and pear (Pomaceae family).

CASE 2.—L. B., male, no occupation, aged twenty-two years, has fall hay fever and asthma together with a constant generalized itching of skin (eczema) which has been growing worse for the past two years. His grandfather was asthmatic. A brother and sister had infantile eczema and now have hay fever. His father and mother have hay fever. Upon eating apple he has swelling of mouth, tongue, and severe generalized urticaria. After eating pear or quince he has the same symptoms. Skin testing gave marked reaction to apple, pear, quince and ragweed confirmed by passive transfer. (Table II.)

TABLE II

PATIENT L. B., SENSITIVE TO APPLE, QUINCE, PEAR, AND RAGWEED

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Apple	2+
		2	Quince	4+
		3	Pear	3+
		4	Ragweed	4+
Apple	0.16	5	Apple	neg.
		6	Quince	neg.
		7	Pear	neg.
Quince	0.32	8	Apple	neg.
		9	Quince	neg.
		10	Pear	neg.
Pear	0.16	11	Apple	neg.
		12	Quince	neg.
		13	Pear	neg.
		14	Ragweed	4+

Experimental.—Serum from this patient incubated with diluent and injected into a normal recipient gave positive passive transfer reactions to apple, quince, pear and ragweed. When the serum was neutralized to apple extract, it no longer reacted to pear and quince. Absorption tests carried out with quince and pear likewise served to neutralize reactivity to the others. To control the specificity of the reaction a site neutralized to apple and quince by absorption with pear was tested to ragweed. A strong reaction was obtained to ragweed in this neutralized site.

The third case to be presented shows mutual absorption by onion and asparagus.

CASE 3.—E. Q., female, housewife, aged thirty-five years, complains that onions cause sneezing. Canned onion soup also causes sneezing. She has hay fever in the late summer. Skin tests were positive to onion, asparagus and ragweed, confirmed by passive transfer. (Table III.)

Experimental.—Serum from this patient incubated with diluent and injected into a normal recipient gave positive passive transfer reactions to asparagus, onion and ragweed. When the serum was incubated with

asparagus, no reaction was obtained with onion; likewise when the serum was incubated with onion, no reaction was obtained to asparagus. To control the specificity of the reaction, the site neutralized to asparagus by absorption with onion was tested to ragweed. A strong reaction to ragweed was obtained.

TABLE III

PATIENT E. Q., SENSITIVE TO ASPARAGUS, ONION, AND RAGWEED

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Asparagus	2+
		2	Onion	2+
		3	Ragweed	3+
Asparagus	0.32	4	Asparagus	neg.
		5	Onion	neg.
Onion	0.32	6	Asparagus	neg.
		7	Onion	neg.
		8	Ragweed	3+

The fourth case to be presented shows complete absorption to codfish and carp by fish glue but only partial absorption to the others by either cod or carp.

CASE 4.—G. Y., female, housewife, aged thirty-six years, has had severe eczematous type of skin eruption following ingestion of fish. She also has hay fever and asthma in the late summer. Skin tests gave marked reactions to codfish, fish glue and carp, confirmed by passive transfer.

Experimental.—Serum from this patient incubated with diluent and injected into a normal recipient gave positive passive transfer reactions to codfish, carp, fish glue and ragweed. When the serum was neutralized to codfish, it no longer reacted to carp but continued to react to fish glue with, however, a decidedly less intense reaction than the serum

TABLE IV

PATIENT, G. Y., SENSITIVE TO CODFISH, CARP, GLUE, AND RAGWEED

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Codfish	3+
		2	Carp	2+
		3	Fish glue	4+
		4	Ragweed	4+
Codfish	0.32	5	Codfish	neg.
		6	Carp	neg.
		7	Fish glue	2+
		8	Ragweed	4+
Carp	0.32	9	Codfish	2+
		10	Carp	neg.
		11	Fish glue	4+
		12	Ragweed	4+
Fish glue	0.32	13	Codfish	neg.
		14	Carp	neg.
		15	Fish glue	neg.
		16	Ragweed	4+

plus diluent. The serum neutralized to codfish continued to give the same intensity of reaction to ragweed as in the case of serum plus diluent. When the serum was neutralized with carp, it continued to react to codfish but with less intensity than the serum plus diluent. These sites tested with fish glue and ragweed continued to react with the same intensity as the serum plus diluent mixtures. When the serum was neutralized with fish glue, it no longer reacted to codfish and carp but continued to react with undiminished intensity to ragweed, showing the specificity of the reaction.

The fifth case to be presented shows partial absorption of wheat and rye by each other.

CASE 5.—G. Y., female, housewife, aged thirty-six years, is the same patient as in the preceding history. In addition to fish sensitivity causing a skin rash she has had eczema, bronchial asthma and hay fever since three years of age. Her husband is a baker. Ingestion of wheat or rye will cause her skin to itch, and handling her husband's work clothes will cause her hands to break out. Inhalation of flour dust causes asthma. Skin testing gave markedly positive reactions to extracts of rye, wheat and ragweed, confirmed by passive transfer. (Table V.)

TABLE V

PATIENT G. Y., SENSITIVE TO WHEAT, RYE, AND RAGWEED

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Wheat	3+
		2	Rye	3+
		3	Ragweed	4+
Wheat	1.6	4	Wheat	neg.
		5	Rye	1+
		6	Ragweed	4+
				±
Rye	1.6	7	Wheat	+
		8	Rye	neg.
		9	Ragweed	4+

Experimental.—Serum from this patient incubated with diluent gave definitely positive reactions to wheat, rye and ragweed. When the serum was neutralized to wheat, the site reacted to rye to only a mildly positive reaction. It continued, however, to give the same positive reaction to ragweed as with the diluent. When the serum was neutralized to rye, the site reacted to wheat to only an equivocal reaction, continuing to give the same positive reaction to ragweed with the diluent, thus showing the specificity of the reaction.

The final case to be presented, like the preceding one, shows partial absorption of wheat with rye and vice versa and also shows the influence of different testing materials on the extent of absorption. It is important to bear in mind in connection with these two experiments that

whereas in Wheat A and Rye A the nitrogen content was the same, namely, 1.6 mg. per c.c., in Wheat B and Rye B the nitrogen content varied, being 0.82 mg. per c.c. for Wheat B and 0.52 for Rye B.

CASE 6.—B. K., male, baker, aged forty-two years, has had asthma for over a year. At the bakery, flour dust aggravates his condition. He states that rye flour is more irritating than wheat flour. Skin tests gave positive reactions to wheat and rye, confirmed by passive transfer. (Tables VI and VII.)

TABLE VI

PATIENT B. K., SENSITIVE TO WHEAT AND RYE

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Wheat A	4+
		2	Rye A	4+
		3	Ragweed	3+
Wheat A	1.6	4	Wheat A	neg.
		5	Rye A	1+
		6	Ragweed	3+
Rye A	1.6	7	Wheat A	1+
		8	Rye A	neg.
		9	Ragweed	3+

TABLE VII

PATIENT B. K., SENSITIVE TO WHEAT, AND RYE

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Diluent		1	Wheat B	4+
		2	Rye B	2+
		3	Ragweed	3+
Wheat B	0.82	4	Wheat B	neg.
		5	Rye B	neg.
		6	Ragweed	3+
Rye B	0.52	7	Wheat B	3+
		8	Rye B	neg.
		9	Ragweed	3+

Experimental.—Using wheat and rye extracts A, the serum when incubated with diluent and a ragweed positive serum gave markedly positive reactions to wheat, rye and ragweed. When the serum was neutralized to Wheat A, the reaction to Rye A was markedly diminished, the reaction to ragweed remaining the same as with the diluent. When the serum was neutralized with Rye A, the reaction to Wheat A was markedly diminished, but the reaction to ragweed remained the same as with the diluent, showing the specificity of the reaction.

Using Wheat and Rye extract B the serum when incubated with diluent and a ragweed positive serum gave markedly positive reactions to Wheat B and ragweed. The reaction to Rye B, while definitely positive, was less intense than in the preceding experiment using Rye A. When the serum was neutralized to Wheat B, the reaction to Rye B was nega-

tive, the reaction to ragweed remaining the same as with the diluent. When the serum was neutralized to Rye B, the reaction to Wheat B, while definitely less than with the diluent, was still very definitely positive, i.e., three-plus as opposed to four-plus with the diluent. The reactivity to ragweed remained the same, thus showing the specificity of the reaction.

The final experiment was performed to demonstrate further the specificity of the reactions obtained in the foregoing.

Experimental.—Serum from Case I (O. B.) sensitive to carrot, celery, parsley and parsnip was mixed equally with serum from Case 2 (L. B.) sensitive to apple, quince, pear and ragweed. The mixture of serum when incubated with ragweed failed to react to ragweed but continued

TABLE VIII

PATIENT O.B., SENSITIVE TO CARROT, CELERY, PARSLEY, AND PARSNIP
PATIENT L. B., SENSITIVE TO APPLE, QUINCE, PEAR, AND RAGWEED

SERUM INCUBATED WITH	NITROGEN MG. PER C.C.	SITE	TESTED TO	RESULT
Ragweed	0.1	1	Carrot	4+
		2	Apple	2+
		3	Ragweed	neg.
Carrot	0.32	4	Carrot	neg.
		5	Apple	2+
		6	Ragweed	3+
Apple	0.16	7	Carrot	4+
		8	Apple	neg.
		9	Ragweed	3+

Experiment combined two sensitive serums in equal portions.

to react to carrot and apple. The mixture of serum when incubated with carrot failed to react to carrot but continued to react to apple and ragweed. The mixture of serum when incubated with apple failed to react to apple but continued to react to carrot and ragweed. (Table VIII.)

COMMENT

It is believed that the above experiments show the close relationship of the atopens in botannically related foods. We realize that these cases consist of isolated instances and that conclusions of too general a nature cannot be drawn. On the other hand, the only criteria for the selection of these cases have been the definiteness of clinical sensitivity, positive skin tests and the presence of reagins in the blood. In all these, partial or complete absorption to other members of the group have been shown to exist.

The implications of this work seem to us to lie in the matter of improving the materials for food testing. The variations in the technic of making extracts, the differences in concentration together with the large number of pseudoreactions in food testing have made for unreliability

in food testing in general. This has caused a widespread skepticism concerning the validity of skin testing for foods. The present paper, while primarily concerned with mutual absorption tests in related foods, at the same time emphasizes the reality of food sensitivity. The work of Ratner[8] showing the immunologic specificity of cow and goat milk lactalbumin, whereas casein seems to be alike in the milk of both species, taken together with the present paper emphasizes the importance of further chemical studies to isolate the important atopens in their purified state. The fact that there are probably closely related atopens in groups of foods should help to facilitate the working out of this problem.

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DISCUSSION

DR. A. STULL, New York.—The serums from these cases in the paper presented by Dr. Baldwin and Miss Benedict offer an interesting opportunity to study skin reactions related to clinical sensitivity to certain common foods. The work has indicated a relationship between the antigens in these groups of foods, and I hope it may be possible for them to continue the work with special attention to chemical separation and purification of the antigens from these materials. As Dr. Baldwin has suggested, I believe more satisfactory results will be obtained with purified antigens. Only by a quantitative chemical and biologic study in these absorption experiments will it be possible to determine whether a single antigen is involved or closely related antigens of similar composition but not identical. Wells and Osborne have shown that chemically identical proteins from biologically unrelated species gave identical immunologic reactions, and chemically different proteins from the same species gave different immunologic reactions, showing that immunologic specificity depended upon chemical structure rather than upon biologic relationship.

Since considerable chemical work has already been done on the separation and identification of the proteins from cereals, the serums and the cases with sensitivity to wheat and rye seem to offer excellent material for further work along these lines.

DR. FRANCIS M. RACKEMANN, Boston.—I should like to ask Dr. Baldwin whether his sensitive serums were tested on more than one recipient at a time.

DR. BALDWIN.—They were, Dr. Rackemann, on more than one recipient.

DR. J. A. CLARKE, JR., Philadelphia.—We made a report before this Society at Albany, many years ago, on a similar work but Dr. Coca persuaded us not to publish it. At that time, we thought we had found

two different types of reagin. I have forgotten the exact substances that we were working with, but they were all inhalants, and a great many of them were pollens. We found when the reagin was present in a weak concentration, like a good many of Dr. Baldwin's two-plus and three-plus reactions, that they were subject to "neutralization" by almost anything. They were very labile, so to speak, whereas the four-plus reactions (where the reagins were present in sufficient concentration so that two, three or more skin tests were necessary to neutralize) were very stable. No matter what was done in the test tube or in the skin, the stronger reaction persisted. On the other hand, when the reagin was in weaker concentrations, it was very easily destroyed. I think there might be something that is nonspecific in Dr. Baldwin's results. If he had used serums with a stronger concentration of reagin, he might have had different results.

Dr. Joseph Harkavy, New York.—I want to endorse what Dr. Clarke has said. Dr. Baldwin's paper is of special interest to me, inasmuch as we have published similar observations.

We also found that wherever there is a positive skin reaction to ragweed associated with a large quantity of corresponding reagin, the latter seems to blot out many heterologous reagins simultaneously present in the same serum. In order to obtain a clear idea of the reagin picture in a serum under investigation, titration of each of the existing reagins according to the method employed by Witebsky and me, will give an insight as to their character and concentration.

Dr. Baldwin.—I am grateful for this discussion and in particular to Dr. Stull who read this paper before its presentation.

In reference to Dr. Clarke's question which he raised concerning the definiteness of these reactions, notably those marked two-plus, all that I can say is that where there was a reaction it was perfectly definite and unequivocal. If the urine of a diabetic person is reported two-plus in sugar, one does not question whether glucose is present, and in the reports made in this paper the plus signs are used to indicate the intensity of a positive reaction. The question of nonspecific neutralization has been pretty well ruled out, I believe, by varying the different components in the absorption solutions and in the testing.

I think Dr. Harkavy's point about the titration of each reagin is an important one. Our object in this paper has been more along qualitative lines to emphasize the fact that in foods, particularly those related botanically, there are related components. Were it not for the fact that in these patients very definite clinical as well as immunologic sensitivity existed, the reactions might not have been so definite. The next step, it would seem to us, is to elaborate and analyze the various components chemically so that more definite information may be obtained about the reactive substances in foods.

EFFECT OF TREATMENT ON SKIN AND MUCOUS MEMBRANE SENSITIVITY AND ON REAGINS IN HAY FEVER*

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WHEREAS the value of preseasonal inoculations with pollen extracts for the treatment of hay fever is now firmly established; there has been no satisfactory method devised to gauge objectively the results of treatment; therefore the statement of the treated individual has had to be accepted as the only therapeutic index. This fact has forced the allergist to analyze the patient's symptoms, comparing the treated with the untreated years. For this purpose he has had to take into consideration not only the duration of the hay fever, its severity, and the number of symptomless days during the pollinating season but also seasonal variations in pollination.

Attempts have been made, however, to determine what changes occur following a course of pollen inoculations. Cooke and VanderVeer[1] found no lessening in the degree of sensitivity of the skin and conjunctivae in individuals who were completely relieved by preseasonal treatment with pollen extracts. On the other hand, Walker[2] reported that in 100 cases of cured hay fever the cutaneous test with the offending pollen was changed from markedly positive to negative in 22 cases. In 22 others the cutaneous test was only very doubtful at the time treatment was discontinued. In the remaining cases there was a marked decrease in skin sensitivity in 12 instances, and no change in 44. Walker[3] also noted that in a series of patients who received adequate treatment for hay fever, there often resulted a marked reduction in the intensity of the skin test. Judging from Walker's observations, however, the skin reaction is not consistently affected by specific treatment. It therefore appears that an individual may be benefited by treatment with a reduction of mucous membrane sensitivity without a corresponding decrease in cutaneous sensitivity.

Levine and Coca[4] were moreover able to demonstrate that following specific pollen treatment there was often no change, and in some cases a quantitative increase of the circulating reagins originally discovered by Prausnitz and Küstner.[5] They used this fact as proof that desensitization cannot be involved, because in a true desensitization if the

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reagins were comparable to anaphylactic antibodies of experimental animals they would be greatly reduced or absent. Chant and Gay[6] also found a quantitative increase of the circulating reagins in one case benefited by preseasonal treatment for hay fever; and Cooke, Bernard, Hebald, and Stull[7] noted that the amount of skin sensitizing antibody in the serum remained practically unchanged by specific injections. From these studies it can be concluded that changes in reagin content of the serum of hay fever patients cannot be used as a guide for the result of treatment.

Since the skin is an unsatisfactory therapeutic index in hay fever, and since the reagins cannot be used for this purpose, it occurred to one of us (Baldwin[11]) a few years ago that the mucous membranes of the nose might be used as such, and that a quantitative study might be made of the decrease in mucous membrane sensitivity by direct application of pollen to the nose. By this method it was thought that some valuable information might also be obtained from a diagnostic and prognostic standpoint. Blackley[8] in 1867 used the mucous membrane route as well as other methods to determine the existence of pollen sensitivity. MacKenzie[9] in 1922 treated a series of patients by spraying pollen solutions into the nose directly. Starting with very weak solutions he was able to show unmistakable evidence of increasing tolerance. In several instances patients were able eventually, after eight to ten weeks of spraying, to use freely a solution 1,000 times stronger than the one which at the onset had caused symptoms even when used in very small amounts. Black[10] in 1925 used the nasal reaction to pollen as a satisfactory standard for measuring the activity of extracts. These were introduced into the nose in increasing amounts until sneezing was produced. He further found that when this was done in the part of the year when there was no pollination, and when there was no nasal irritation from other causes, the minimal amount of a given extract necessary to produce symptoms was exceedingly constant. Sneezing with this dose would begin within five minutes, and if a certain concentration of a given solution was required on a given day, the same amount of that extract would produce the same reaction on any other day. This has also been our experience in the use of pollen extracts in the nose. That is to say, patients react in the same way to a given amount and a given concentration of pollen extract when it is instilled in the nostril from day to day. One of us (Baldwin[11]) used pollen extracts successfully to detect the early appearance of mucous membrane sensitivity in a small series of individuals who had a direct inheritance of hay fever but who at the beginning of the studies were not as yet suffering from any form of hypersensitiveness.

In the present series of 98 cases a systematic study before and after treatment was made of the skin test in 93, of mucous membrane reac-

tions in 85, and of the reagin content of the serum in 8 in an attempt to find out whether or not an objective index could be found for therapeutic results.

PREPARATION OF MATERIAL

In order to obtain satisfactory pollen extracts of uniform strength, the pollen was accurately weighed, 2 gm. being used per 100 c.c. of extracting fluid. The latter consisted of the sodium bicarbonate solution advocated by Coca[12] which is of such strength that, with the use of methyl orange as an indicator, 10 c.c. of the final fluid is neutralized by 3 c.c. of N/10 acid. Phenol was added as a preservative. This solution was found to be satisfactory for pollen extraction, since it gave extracts of uniform potency. Nitrogen determinations were made on the extract before the beginning of treatments and again at their completion. The potency of the extracts was tested throughout the time they were being used. This was determined by performing skin tests with different concentrations of the extracts, at different intervals during the pollinating season upon hypersensitive individuals who had sensitive skins but who were not receiving specific treatment.

The extract of timothy 1:50 was found to contain 0.35 to 0.4 mg. nitrogen per cubic centimeter before treatment, and it did not vary to any measurable degree during the few months it was being used for the studies. On one subject, H. T., tested with the extract because he was not receiving treatment, the cutaneous test with the timothy extract showed a disappearance point of 1:10,000 in March, soon after the extracts were made, and the same disappearance point in June. The same tests for potency were carried out with the other pollen extracts used in these experiments. Therefore, neither by nitrogen determinations nor by skin tests on hypersensitive individuals could any alteration of the extracts be demonstrated during the time they were being employed. Furthermore, it should be emphasized that the same stock solution and the same stock dilutions were used throughout for the experiments. In this way it was thought that sources of error from possible varying strengths of extracts might be eliminated. Great care was also taken with the syringes, glassware and needles; they were not only washed in many changes of water, but as far as possible a sufficient number were used so that the same implements were employed for given dilutions. By taking these precautions it was found possible to prevent confusing results from the more concentrated extracts becoming mixed with the more dilute.

COMPARISON OF THE CUTANEOUS TESTS BEFORE AND AFTER TREATMENT

In the present study, 93 individuals treated for summer and autumn hay fever were skin tested before treatment was begun and after the completion of treatment. This series comprised a typical group of cases

with average results from preseasonal treatment. In the grass sensitive cases all the important eastern grasses which cause hay fever were first employed, but in view of the observations of Stull, Cooke and Barnard[13] and others, and from our own experience, timothy alone was eventually selected because in the East it apparently represents the principal of-

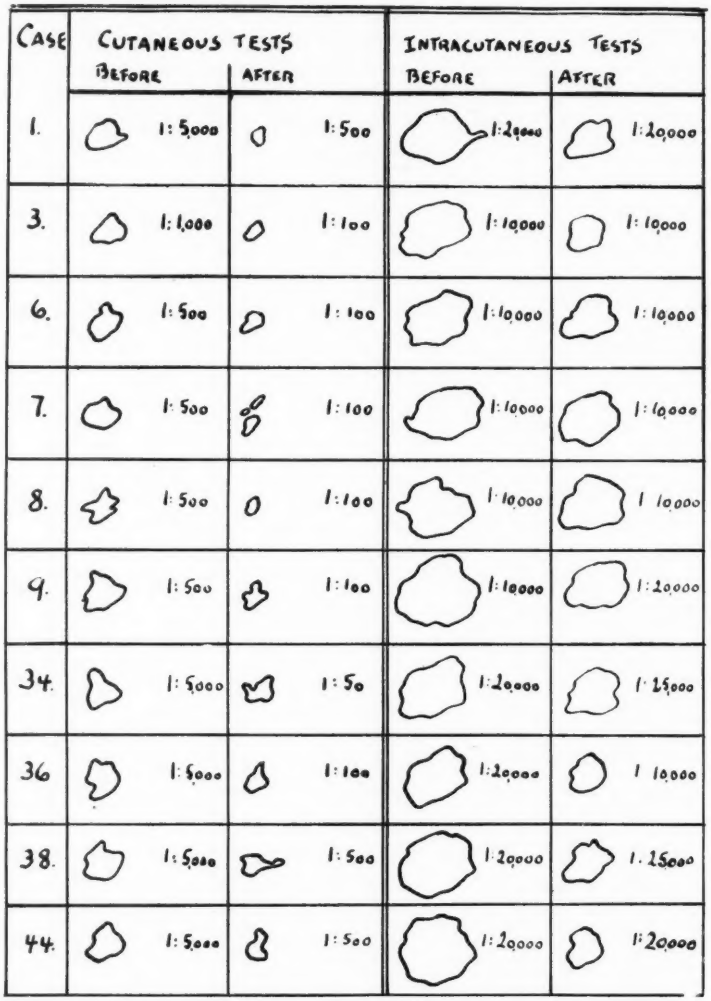

Fig. 1.—Comparison of cutaneous and intracutaneous tests before and after treatment for hay fever. Results are expressed in terms of last wheal formation before the disappearance point.

fender in a group sensitivity of the grasses, just as ragweed is an important member of the compositae family.

In performing the skin tests, at first both the scratch and the intradermal methods were used, but it was found that by the intradermal method it was difficult to detect the disappearance point of the reaction. In cases tested which showed a marked reduction in sensitivity by the

scratch method following treatment, there was also apparently a reduction demonstrable by the intradermal method, although the difference in the latter before and after treatment was usually so indefinite as to leave some doubt as to the true significance of the slight differences observed. This discrepancy noted between the two methods of testing is apparently due to the fact that the intracutaneous test is so much more delicate than the cutaneous that a positive reaction has a less sharply defined end point with succeeding dilutions of the pollen extract. In none of the present series of cases was there a complete disappearance of the skin reaction by either method of testing, although in many instances the differences recorded before and after treatment were striking. The results obtained by both methods of testing in 10 cases are shown in Fig. 1.

Table I illustrates the results of treatment; these compared favorably with the results of others such as Cooke and VanderVeer,[14] Walker,[3] and Rackemann.[15]

TABLE I

CLINICAL RESULTS OF TREATMENT IN THE 98 CASES

	NO.	PER CENT
Marked improvement	64	65.3
Moderate improvement	18	18.3
Unimproved	16	16.3

The treatments consisted of a series of 14 to 20 subcutaneous inoculations of progressively increasing concentrations of pollen extract, given from one to three times a week. The whole course of treatments was completed in most of the cases before the beginning of the pollinating season. Starting with a concentration of 1:5,000 or higher dilutions, depending upon the case, the individual doses were progressively increased until a given amount of the 1:500 or even 1:100 strength had been reached.

TABLE II

CUTANEOUS REACTIONS AT THE COMPLETION OF TREATMENT

	CASES		SKIN SENSITIVITY			
			DECREASED		UNCHANGED	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
All cases	93		61	77	32	23
With clinical improvement	79	84	54	68	25	32
Without clinical improvement	14	16	7	50	7	50

As shown in Table II, 61 of the cases tested showed a decrease in the cutaneous reaction following treatment. Only 54 of the 79 patients improved by treatment, however, showed a reduced skin sensitivity; the remaining 25 showed no change. It is interesting to note that of the 14 patients unimproved by treatment 7 showed a definite reduction in

the cutaneous reaction. Our findings do not bear out Walker's observations that in general there were better symptomatic results and greater reduction in the skin sensitivity in those cases having received the greater amount of treatment. In some cases there were adequate treatment and marked improvement but no demonstrable change in the skin test; while in others the reactivity of the skin was reduced, whereas there was practically no improvement from the course of treatments.

From our studies, therefore, it may be concluded that the skin reaction cannot be used as an index of the value of preseasonal treatments in hay fever. To be sure, it is frequently decreased in those cases that are benefited but it is often unchanged, and there may even be a lessened skin sensitivity without any demonstrable clinical improvement.

COMPARISON OF MUCOUS MEMBRANE SENSITIVITY BEFORE AND AFTER TREATMENT

Although the skin reaction is not consistently decreased in individuals benefited by preseasonal treatments with pollen extracts, it was assumed that in these cases the mucous membranes are rendered less sensitive, and therefore that preseasonal direct application of pollen extract to the nasal mucous membrane would demonstrate a lowered sensitivity following a course of treatment. In order to demonstrate as accurately as possible this change in mucous membrane sensitivity, uniformity in method of testing was necessary. For this purpose at first a given amount of a given dilution of pollen extract was instilled into the nostrils of 85 patients as advocated by Black. Later it was found simpler to use sprays. A standard DeVilbis atomizer was used, and the given concentration of extract was sprayed into the nostril in a uniform manner. Each concentration from 1:100,000 to 1:500 was kept in a separate sterile container, and a separate atomizer was used for each dilution. The test consisted of spraying the nostril with six full squeezes of the bulb. The patient was then observed for one-half hour. In all cases a dilute solution was at first used, and if no reaction was obtained the concentration was increased until sneezing, lacrymation and coryza occurred. It sometimes required several days of testing before the reaction point could be determined, because it did not seem justifiable to use many different concentrations in the nose on the same day, as by this method a cumulative reaction might be obtained from repeated testing. The symptoms resulting from this method of testing were those of hay fever, and varied in intensity with the concentration of the pollen extract employed. After considerable experimenting the ideal positive reaction was found to be that giving mild symptoms of coryza and slight nasal congestion, usually appearing within five to ten minutes, and if untreated, lasting about one hour. When more violent reactions were obtained, the dilution was increased until only mild symptoms developed

following the instillations. It is important not to mistake the initial mild irritation following the instillations for positive reactions; this differs from the latter in that it occurs at the time of the instillations and lasts but a few seconds. The positive reactions are occasionally delayed in their appearance for an hour or longer after the mucous membrane has been sprayed; in some of these cases violent symptoms of coryza, sneezing and lacrymation occur so that it cannot be concluded that the appearance time of the symptoms is in itself an indication of the degree of mucous membrane sensitivity. Moreover, reactions were at times delayed even when solutions were used far beyond the concentration necessary to produce symptoms. Thus in one case the patient was tested in the forenoon and claimed that he first began having violent symptoms at about 3 P.M. These lasted for two hours until an ephedrine spray gave prompt relief. In this respect it is to be noted that the reactions produced by instillation of pollen can always be readily relieved by spraying the nostrils with a 2 per cent solution of ephedrine.

Eighty-five patients were tested before treatments were instituted and again at the completion of a course of inoculations. Care was taken to test the mucous membranes the second time before the expected pollination of the offending grasses or ragweed. When the air was once filled with pollen responsible for hay fever, it was felt that the test of mucous membrane sensitivity by the spray method would be of no value, for it would be impossible to determine whether or not the symptoms were in part due to the presence of pollen in the inhaled air.

TABLE III

MUCOUS MEMBRANE SENSITIVITY AT THE COMPLETION OF TREATMENT

	NO. OF CASES	PER CENT	MUCOUS MEMBRANE SENSITIVITY					
			DECREASED		UNCHANGED		INCREASED	
			NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
All cases	85		80	94	4	4.7	1	1.3
With marked improvement	55	64	55	100	0		0	
With moderate improvement	16	19	16	100	0		0	
Without improvement	14	17	8	57	5	35	1	8

As will be seen in Table III, of the 85 tested, the mucous membrane sensitivity was decreased in 80, unchanged in 4, and actually increased in 1. In 55 of the cases in which the mucous membrane sensitivity was decreased there was marked improvement; in 16 more there was moderate improvement; whereas in 9 there was no improvement. In all cases benefited by treatment there was a decreased mucous membrane sensitivity, but in 9 cases without clinical improvement there was also a decreased sensitivity. It is interesting to note that in one unimproved patient there was increased mucous membrane sensitivity. This would

tend to indicate that in rare instances treatment may possibly be responsible for rendering a patient more rather than less pollen sensitive. If this type of study were to be made in a larger group of individuals from year to year, and particularly in those who persistently do not respond to treatment, possibly this unexpected result from the inoculation treatment of hay fever might be frequently discovered.

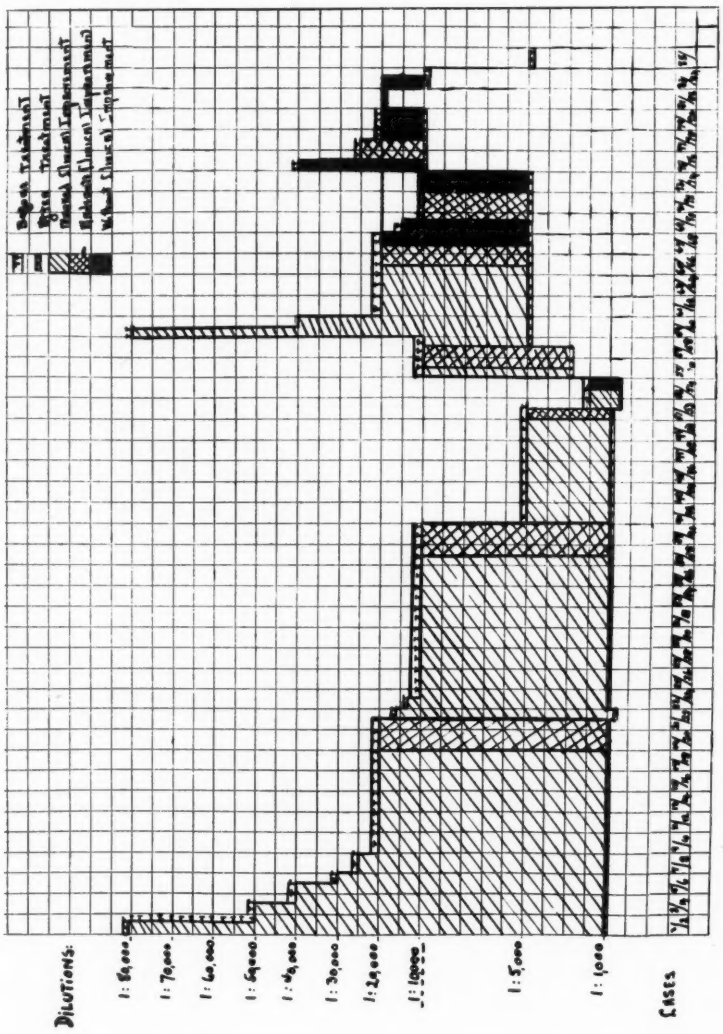

Fig. 2.—The amount of decreased mucous membrane sensitivity following treatment.

Upon analysis of the mucous membrane sensitivity at the end of a course of treatments (Fig. 2) it was found that in general those cases were benefited in which the pollen spray produced symptoms only in concentration of 1:1000 or less. There were 8 exceptions, however, in 3 of these; although mild irritative symptoms were obtained with pollen dilutions of 1:5000 immediately before the starting of the hay fever

season, marked improvement was obtained from treatment as evidenced by the fact that these patients had from 75 per cent to 85 per cent less hay fever than in the untreated years. Two more cases were moderately benefited by treatment in which the final dilution producing symptoms was 1:10,000. On the other hand, there was one case unimproved by

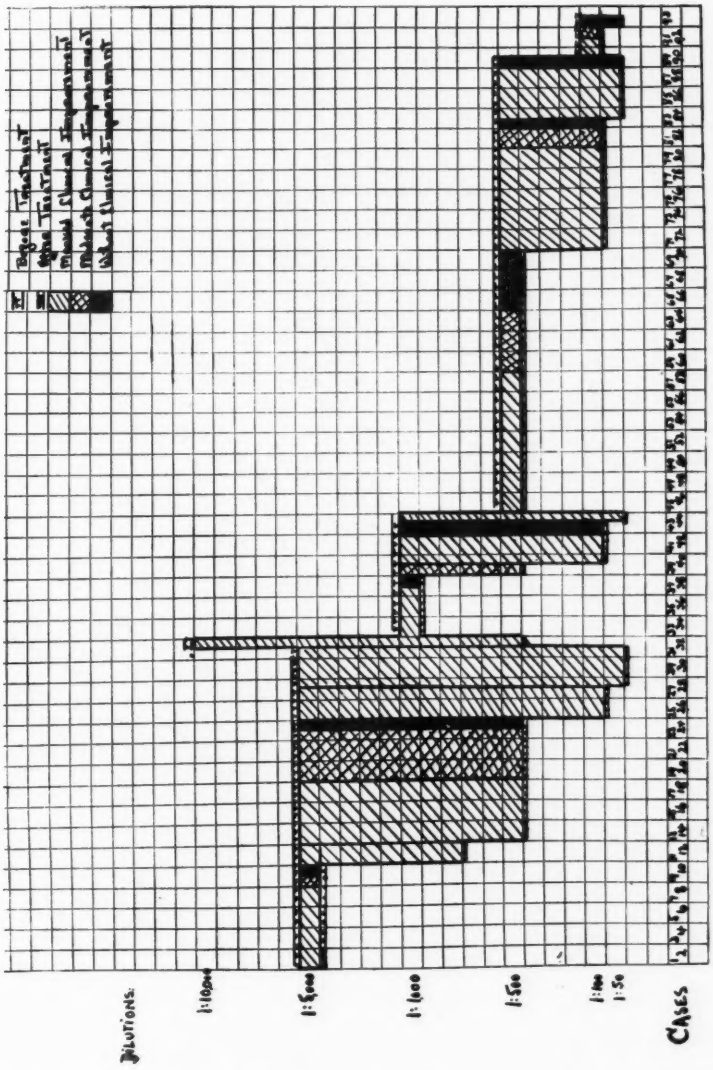

Fig. 3.—The amount of decreased skin sensitivity following treatment.

treatment which gave a final mucous membrane reaction point of 1:1000 or less. It is difficult to explain these exceptions to the general rule, for upon careful analysis of the factors of environment and seasonal variations in pollination no adequate reason could be found. A possible explanation for the lack of correlation between the mucous membrane sensitivity and the subjective amount of improvement from hay fever

treatment lies in the fact that patients vary in their emotional reaction to symptoms. Some individuals are completely prostrated by the mildest hay fever; whereas others with a far more violent form are able to carry on their activities without much difficulty.

There seems to be some relationship between the amount of decreased mucous membrane sensitivity as determined by the difference between the test before and after completion of treatment and the benefit of treatment, for in the 8 cases in which the final reaction point was 1:5,000 the initial reaction was obtained with a 1:20,000 dilution or greater. There were also 10 cases greatly improved, in some of which the decreased sensitivity moved only in the narrow range between 1:5,000 and 1:1,000.

There is absolutely no correlation between the skin and the mucous membrane reactions, for there were many cases in which the skin tests remained unchanged following treatment but which showed a marked decrease in mucous membrane sensitivity.

In general one may conclude from these studies that treatment with specific pollen extracts more often produces a change in the mucous membrane than in the skin reaction. For in the 85 cases studied the mucous membrane sensitivity was altered in 80; whereas in the 93 cases studied there was altered skin reactivity in only 61. There was an altered mucous membrane reaction in all the cases improved by treatment, but the skin reaction was decreased in only 54 of the 79 cases improved by treatment.

QUANTITATIVE STUDIES OF REAGIN CONTENT OF ATOPIC SERA BEFORE AND AFTER TREATMENT

Eight patients were studied for the reagin content of the serum before and at the end of a course of treatment, as will be seen by referring to Table IV. All but one of these patients was strongly positive by the

TABLE IV

CLINICAL ANALYSIS OF 8 CASES IN WHICH REAGIN CONTENT OF SERUM WAS MADE BEFORE AND AFTER TREATMENT

CASE	SKIN REACTIONS		MUCOUS MEMBRANE REACTIONS		
	BEFORE TREATMENT	AFTER TREATMENT	BEFORE TREATMENT	AFTER TREATMENT	RESULTS OF TREATMENT
F.	T 1: 500	T 1: 50	T 1:20,000	T 1: 1,000	80% improvement
A. H.	T 1: 500	T 1: 50	Not done	T 1: 5,000	75% improvement
P. R.	T 1:5,000	Not done	T 1:10,000	T 1: 1,000	50% improvement
M.	T 1:5,000	T 1:500	T 1:20,000	T 1: 1,000	80% improvement
J. B.	T 1:5,000	T 1:500	Not done	Not done	50% improvement
S. H.	T 1: 500	T 1: 50	Not done	T 1: 5,000	25% improvement
S.	T 1: 500	T 1:100	T 1: 5,000	T 1: 500	80% improvement
McA.	T 1: 100	T 1:100	T 1:25,000	T 1:10,000	50% improvement

scratch method before treatment was started. In 6 of them the skin reactivity was markedly decreased following a course of treatment. In the seventh case the skin test was not repeated at the end of a course of

inoculations, but the mucous membrane sensitivity was decreased in this case from 1:10,000 to 1:1,000. In the eighth case there was no change in the skin and only a mild decrease in mucous membrane reactivity. In this group there was a 50 per cent or better clinical improvement over untreated years except in one case. A patient who is 50 per cent improved has only a few bad attacks of hay fever and long periods of freedom. The season of active symptoms is moreover shortened to about one-half its usual length. In none of this series was there 100 per cent good results, for even in the most favorable cases there were a few days of mild coryza and other hay fever symptoms. In some instances the hay fever started promptly and severely early in the season but lasted only a few days, after which there was complete freedom from symptoms.

In the selection of normal non-sensitive individuals for passive transfer experiments, only those with strongly receptive skins were chosen. A test of receptivity was made by injecting intracutaneously 0.15 c.c. of a 1:32 dilution of the serum obtained from the 8 patients used in this study. A few days later 0.1 c.c. of a concentrated pollen extract was injected into the locally sensitized sites. Having established that the recipient was suitable for passive transfer, 0.15 c.c. of concentrated serum, obtained from one of the patients before initiation of hay fever treatment, was injected into the inner surface of the right forearm. Beginning at the elbow five separate sites were sensitized from above downward. Two days later a high dilution of pollen extract was injected into the uppermost sensitized site. If at the end of ten minutes no reaction was noted, the next lower site was tested with a more concentrated solution, and so on until a positive reaction was obtained; this was recorded as the appearance level for the passive transfer with this serum. A few days later, on the inner surface of the left forearm five sites were similarly sensitized from above downward, but this time dilutions of the serum were used. In the uppermost site a 1:1,024 dilution was used, and progressively downward were injected in increasing concentrations, 1:512, 1:256, 1:128, and finally 1:64. Occasionally an additional passive transfer was made with a 1:32 dilution. Two days later a concentrated pollen extract was injected into the five sites, and the readings were made within ten to fifteen minutes. The above technic was followed in order to prevent spreading from one to the other sensitized site by way of the lymphatics or blood stream. When dilutions of the pollen extract were used, it was found to be more practicable to test each site separately, waiting a suitable time for the appearance of a reaction before testing the next site, since it was discovered that by this method the extract did not spread to involve adjacent sensitized sites; on the other hand, when concentrated extracts were used for testing, adjacent sensitized areas reacted even when the extract was injected

into only one site. Therefore, under these conditions the tests of the areas sensitized with varying dilutions of serum had to be made simultaneously, and the readings recorded promptly within the shortest possible time at which reactions occurred. It was also found by experience that different days had to be selected for the local skin sensitization of the two forearms, because the contralateral reactions described by Chant and Gay occurred when both forearms were tested on the same

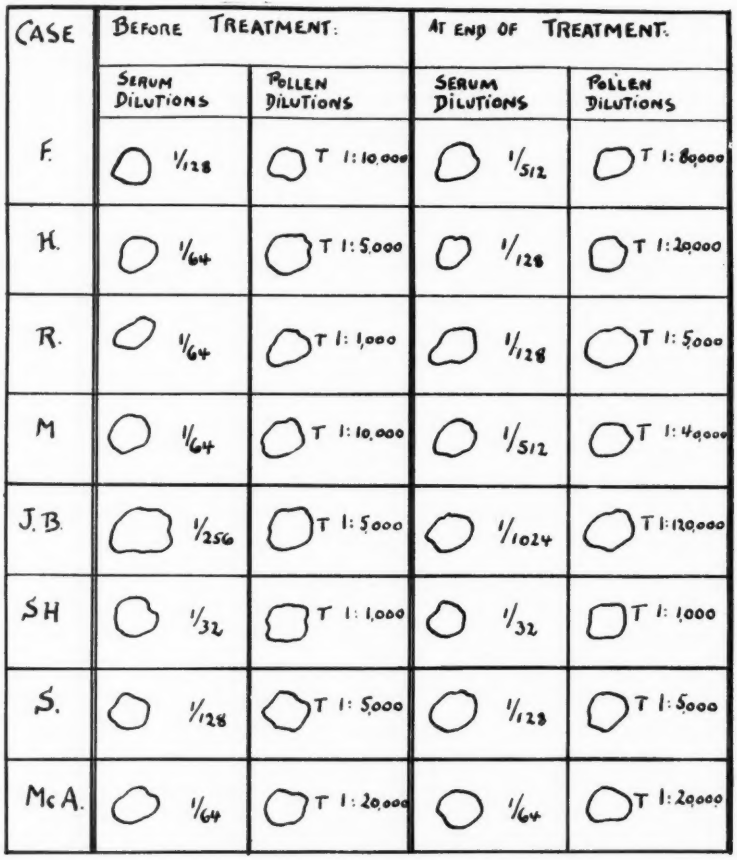

Fig. 4.—Quantitative reagin study by passive transfer method carried out with sera obtained from patients before and after specific pollen therapy. Comparable results were obtained whether the pollen extract was kept constant with serial serum dilutions for the passive transfer or whether with unchanged serum concentration, the pollen extract was varied.

day. In every instance control tests with undiluted serum and concentrated pollen extract were made in order to rule out the possibility of nonspecific reactions. The final reading selected was at the site at which a definite though mild reaction was obtained, below which there was a negative reaction. For instance, testing on the right forearm with a concentrated pollen extract, if there was a wheal with surrounding erythema at the 1:256 site, and none at the 1:512, the former was re-

corded as the disappearance point of the test. Similarly, testing on the left forearm, if a reaction was obtained at the site at which an undiluted serum had been injected with a pollen dilution of 1:5,000 and none in a corresponding similar site with a dilution of 1:10,000, the former was recorded as the disappearance point of the reaction. Upon retesting the recipients with the patient's serum at the end of a course of treatment the same technic was followed except that the outer instead of the inner surface of the forearm was selected for the local skin sensitizations.

By referring to Fig. 4 it will be seen that according to both methods of testing there was a marked increase in the reagin content of the serum following a course of specific pollen treatment in 5 out of the 8 cases. All these patients were improved. On the other hand, out of 3 patients in whom there was no demonstrable increase of the reagin content of the serum, 2 were benefited by treatment and in one of these there was a marked decrease in both skin and mucous membrane sensitivity.

From these few cases it can be concluded that the reagin content of the serum is often increased following a specific course of treatment but that there may be no demonstrable quantitative change in skin sensitizing substances in patients who are clinically benefited by treatment.

SUMMARY

1. In a series of 98 cases of pollen sensitive individuals a systematic study was made before and after specific treatment, of the skin reactions in 93, of the mucous membrane reactions in 85, and of the reagin content of the serum in 8, in order to determine whether changes in skin or mucous membrane sensitivity or in circulating reagins could be used as a therapeutic index.

2. The skin sensitivity was reduced but not abolished following treatment in over half the cases studied. But not all the patients benefited showed reduced skin sensitivity, and in some unimproved cases there was a lowered cutaneous reactivity. Therefore the skin cannot be used as a therapeutic index.

3. Studies of mucous membrane sensitivity showed that following treatment there was always a reduction in those patients who were benefited. In general, the greatest improvement was noted in the cases requiring concentrated extracts to produce symptoms of hay fever, although a few patients were benefited who reacted to relatively high dilutions of pollen extract. Conversely, one patient requiring a highly concentrated extract to produce hay fever symptoms was not benefited by treatment. In one patient not benefited by treatment there was a measurable increase in mucous membrane sensitivity. The mucous membrane of the nose can then in general be used as a therapeutic index in hay fever.

4. There was no consistent correlation between the changes in the skin and mucous membranes following a course of treatment.

5. A quantitative estimation of the reagin content of the serum showed a marked increase following treatment in 5 of the 8 cases studied. These 5 patients were benefited by treatment. Two of the patients showing no demonstrable change in the reagin content of their serum were also benefited by treatment. The skin sensitizing substances cannot therefore be used as a therapeutic index.

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THROMBOCYTOPENIC PURPURA DUE TO FOOD ALLERGY*

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IN APRIL, 1934, Loewy[1] reported a case of thrombocytopenic purpura due to prolonged administration of sedormid (allylisopropyl-acetylurea) in which, after recovery, thrombopenic purpura was produced at will by giving from a half to one 4 grain (0.25 gm.) tablet of the drug. Skin tests in this patient were negative. Peshkin and Miller[2] in May, 1934, reported a case of thrombocytopenia due to ingestion of quinine and ergot. In their patient there was a positive skin and passive transfer reaction to quinine. They cite a similar case reported by Maritschek and Markowicz[3] in which, following "quinine intoxication" during treatment of malaria fifteen years previously, the patient had remained persistently hypersensitive to quinine, so that even small doses (0.3 gm.) produced severe thrombocytopenia.

Since it has been so conclusively shown that thrombocytopenic purpura could be produced by drug hypersensitivity, it seemed to us possible that an allergic response might be the underlying mechanism in many cases of idiopathic thrombocytopenic purpura (Werlhoff's disease) not explainable on the basis of drug allergy, toxic changes or hematopoietic disease. We have observed three patients with primary thrombocytopenic purpura in whom these factors could be excluded, and in our search for etiology, food allergy was considered. These patients were studied accordingly. Following inquiry into food disagreements and associated allergic disturbances, routine cutaneous and intracutaneous testing was done with the usual food and inhalent allergens. Based on history and skin tests, suspected foods were excluded from the diet. Treatment limited to such dietary manipulation was followed by striking clinical improvement and concurrent gradual but marked rise in the thrombocyte level in each.

To demonstrate further the relation of specific foods to the thrombocyte level, hematologic studies were made following ingestion of suspected foods as soon as the clinical condition of the patient justified.

All ingestion tests were made in the morning before breakfast, and care was taken during the test period to avoid postural changes. To establish a base level preliminary counts of total leucocytes, eosinophiles and thrombocytes were made at three 15-minute intervals, and subsequent to ingestion of the test food counts were made at intervals of 15,

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30, 60 and 90 minutes. Eosin-acetone diluting fluid[4] was used, and eosinophile counts were made in the counting chamber simultaneously with and in the usual manner for leucocyte counts. Thrombocyte counts were made in the counting chamber using Diner's solution* for diluting the blood. It is recognized that thrombocyte counts made from day to day show wide fluctuations. Preliminary counts, however, invariably showed close agreement in all three cell types counted. We wish to emphasize that we regard the serial changes in level at any given time as the essential basis for interpretation of the hematologic response.

CASE REPORTS

CASE 1.—L. B., a schoolgirl, aged twelve years, was seen by one of us in December, 1933. Six months previously discoloration of the skin was noticed after slight bruising. In September, 1933, following the extraction of a tooth there was severe hemorrhage from the gums lasting a week. Because of violent epistaxis December 23, 1933, she was taken to a hospital where she remained until January 26, 1934. During this time she presented the typical picture of primary thrombocytopenic purpura with extensive subcutaneous hemorrhages, bleeding from the nose and gums, and occasional pain in the knee joints without swelling. The minimum platelet count at this time was 10,000, the bleeding time was one hour thirty minutes, the coagulation time was within normal limits, and the clot was nonretractile. She was given whole blood by transfusion and intramuscular injections with temporary improvement. After returning home she remained almost constantly in bed until April, 1934. During this time there were occasional small hemorrhages from the nose or gums, and if she attempted to get up the skin would be covered with purpuric spots.

Prior to the onset of the purpura she had frequent severe headaches not associated with nausea. Apart from constipation there had been no gastrointestinal disturbance. Early in the spring of 1934 she developed an urticarial rash.

Her mother had mild purpura at the age of sixteen. A sister has eczema and her maternal grandmother had hay fever.

On Sept. 21, 1934, her blood count was: red blood cells 3,500,000; hemoglobin 55 per cent; white blood cells 5,400; polymorphonuclears 60 per cent; eosinophiles 2.0 per cent; small lymphocytes 35 per cent; monocytes 2 per cent; platelets 13,000. Clot was nonretractile. Many small purpuric spots were present over the extremities and body. At this time routine cutaneous reactions to food and inhalent allergens were essentially negative, but intracutaneous tests showed a strongly positive reaction to strawberry and mildly positive reactions to wheat, potato, cocoa, kidney bean, beet, cantaloupe, cucumber, walnut, raspberry, pear, and banana. Not over six intracutaneous tests were done at one time, and it was noticed that frequently after positive reactions were obtained she felt generally worse and complained of joint pains.

Within a month after the elimination of suspected foods purpuric spots had almost entirely disappeared, and she was able to be out of bed for the first time in a year. The platelet count on March 16 was 74,000, and on April 21 she was allowed potato. On April 23 her platelet count was 68,000, but because the slight fall was not felt to be significant potato was continued. Her mother noticed frequent nausea,

*Diner's solution:

Sod. chloride	0.85
Sod. acetate	2.0
G. azure II	0.001
Formalin	0.2
Dist. water	100.

severe headaches, increased nervousness and crying spells, and because these symptoms previously had regularly preceded an acute purpuric outbreak, she again eliminated potatoes from her diet on May 18 without reporting for blood study. Since that time she has continued in school and has had no recurrence of purpura or bleeding.

In August, 1935, the platelets were between 114,000 and 166,000, the bleeding time was normal, and the clot showed normal retractility. At this time the hematologic response was studied after ingestion of wheat, egg, cocoa, and potato. The response to both egg and cocoa was negative. Wheat ingestion resulted in a typical leucopenic-eosinophilic response, but there was no significant alteration in

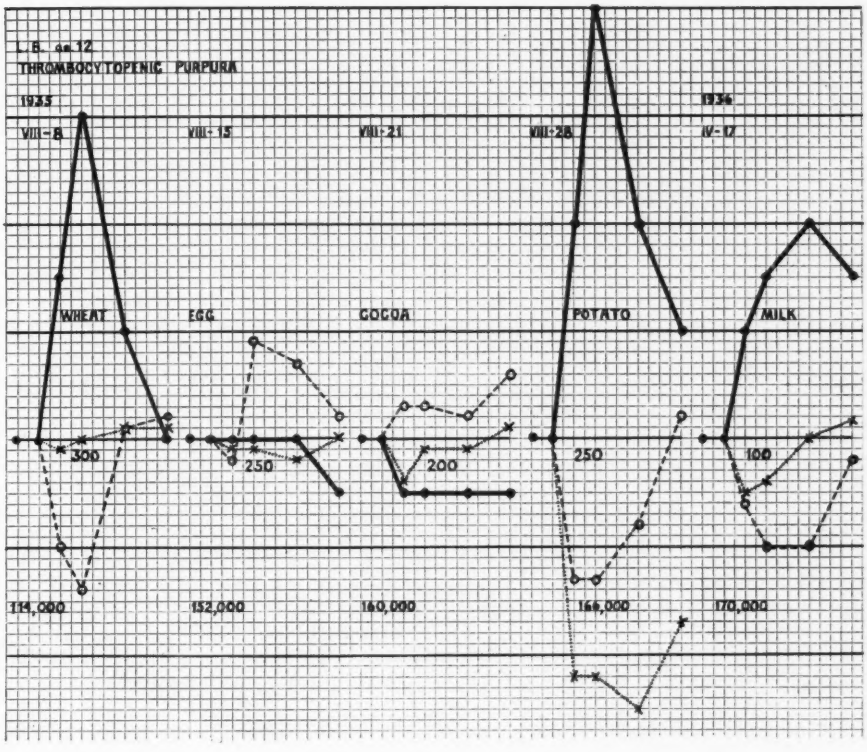

Fig. 1.—Case 1. Positive hematologic response after wheat ingestion without change in thrombocyte level; positive response after potato with marked drop in thrombocytes; positive response after milk without significant change in thrombocytes. Negative response after ingestion of egg and of cocoa.

NOTE: In all graphs thrombocyte counts are represented by dotted lines and crosses, leucocyte counts by dashes and circles, and eosinophile counts by heavy lines and dots. Deviations from pre-ingestion level are recorded. Each horizontal division represents 2,000 thrombocytes, 100 leucocytes and 10 eosinophiles. Two vertical divisions represent fifteen minutes. Upper figures represent the initial level of eosinophiles; lower figures the initial level of thrombocytes.

the thrombocyte level. Following ingestion of potato, in addition to leucopenia and eosinophilia, there was a sharp drop in thrombocytes from 166,000 to 114,000 sixty minutes after ingestion (Fig. 1).

She was not seen subsequently until March 20, 1936. Throughout the winter she had remained well except for headaches which had increased somewhat in frequency. Her mother stated that in spite of occasional rather severe bumps no bruising resulted, and the platelets were found to be 180,000. An extremely carious tooth was extracted on March 24, 1936, with no subsequent bleeding. On April 17 milk inges-

tion showed a definite leucopenic-eosinophilic response without significant alteration in the thrombocyte level. Apparently the headaches have been relieved by subsequent milk elimination.

CASE 2.—M. D., a twenty-six-year-old nurse, single, was seen June 26, 1935, complaining of rectal bleeding and recurrent attacks of right lower quadrant pain.

In January, 1929, thyroidectomy had been done with relief of typical symptoms of hyperthyroidism.

In 1930 she began to have recurrent attacks of nausea and vomiting lasting a few days to three weeks and recurring four or five times each year, and at the same time there were attacks of cramplike abdominal pain followed by watery red bowel

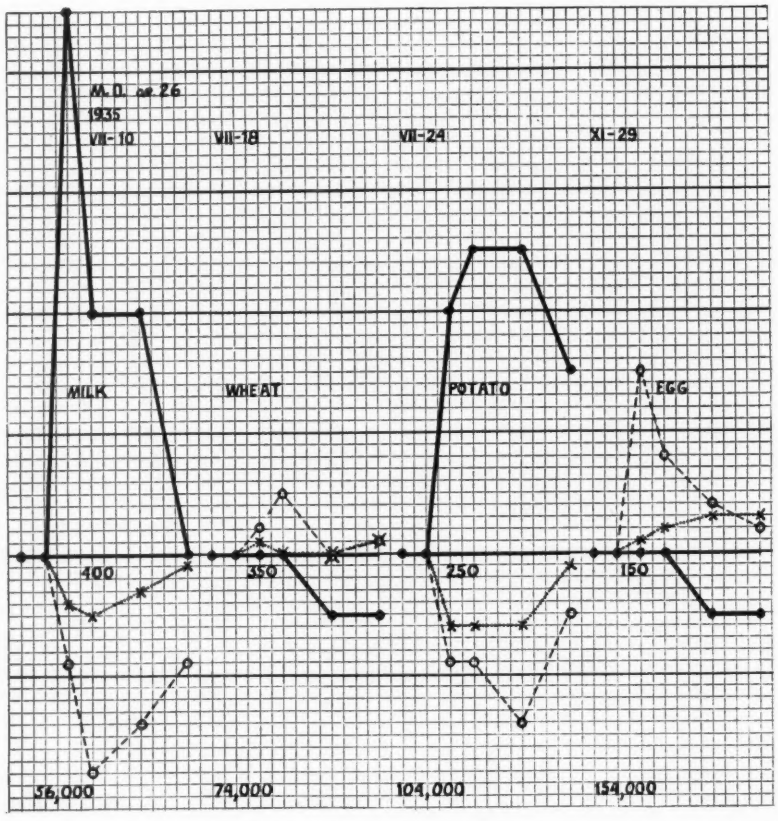

Fig. 2.—Case 2. Positive hematologic response after ingestion of milk and potato with associated suggestive depression of thrombocytes. Response after wheat and egg negative.

movements. Bleeding never lasted more than two days, and between the recurrent attacks there were intervals of freedom lasting from two to four months. In April, 1933, appendectomy was done with no subsequent improvement. At about this time she observed that nausea was always worse after a meal of meat and potatoes. Gas and a feeling of nausea has followed milk ingestion, and after whipped cream or ice cream vomiting occurred regularly.

Proctoscopic examinations in December, 1934, and May, 1935, were negative, and in May, 1935, a cystoscopic examination was negative.

During the winter of 1934-35 she noted almost constant unexplained bruises, and rectal bleeding occurred with increasing frequency. There was no history of asso-

ciated allergic disturbances, and the family allergic history was negative. One sister had had unexplained persistent bleeding after appendectomy.

On June 26, 1935, her blood count showed: white blood cells, 5,550; polymorphonuclears 58; eosinophiles 4.5; basophiles 0.5; small lymphocytes 36; monocytes 1.0; platelets 66,000.

Routine allergic study showed a positive cutaneous reaction to horse serum and intracutaneous positive reactions to potato and banana. On the evening following intracutaneous testing with potato she had a rather severe rectal hemorrhage and also some bleeding from the gums.

On July 10 the platelet count was 56,000, and ingestion test was done with milk. There was a positive hematologic response accompanied by a questionable platelet fall to 46,000 at thirty minutes (Fig. 2). During the test period she complained of general malaise and a dull headache, and there was cramping pain in the mid-epigastrium which lasted about twenty minutes, associated with nausea which continued for the rest of the day. Following milk elimination the platelets had risen to 72,000 on July 18, and at this time wheat ingestion gave a negative hematologic response. On July 24 the platelet count was 104,000, and an ingestion test was done with potato. There was a definite allergic response on the part of the leucocytes and eosinophiles and a suggestive fall in platelets to 91,000 at thirty minutes. Subsequent to potato elimination she felt generally much better, and the platelet count on September 4 was 184,000. In addition to milk and potato which are regarded as major offenders, her food diary and clinical trial have shown that banana, peach, orange, blueberries, and onions cause nausea and abdominal distress.

Since the elimination of potato and milk in July, 1935, repeated platelet counts have never been found below 140,000 save on one occasion when after a period of severe abdominal distress following repeated onion ingestion the count was 122,000. The last platelet count on April 13, 1936, was 190,000, and abdominal symptoms were much improved; although at times she still has distress, especially just before and during the menstrual period.

CASE 3.—R. R., a four-year-old boy with a strong bilateral allergic family history was seen April 5, 1935. Shortly after birth he developed facial eczema which continued until age two years. In October, 1933, he had an attack of asthma, and there have been recurrent attacks since. On March 26, 1935 purpuric spots were observed on his neck, and a little later scattered purpura was present and he was moved to the hospital where he was given whole blood intramuscularly and by repeated transfusions. Epistaxis continued intermittently until April 5. Platelet count on March 29 was 10,000.

On April 8 a partial allergic study was done by passive transfer to the mother. Significantly positive reactions were demonstrated for egg and celery only, although the reactions to a number of foods including wheat were equally strong in both the sensitized and the control sites.

On April 9 a trial diet of nonreacting foods was prescribed consisting of rye, lamb, milk, sweet potato, apricot, banana, beets, and olive oil. Cevitamic acid (cebione) 0.1 gm. was given daily.

On April 16 after he had been making satisfactory progress and the platelets had risen to 56,000, bacon, chicken and baked potato were added to his diet. On April 17 petechial spots were noticed on the neck; on April 26 he had epistaxis; and on April 29 the platelet count was 25,000. He was again taken to the hospital and returned to the original diet. On May 3 the platelet count was 59,000. On May 4 he ate wheat crackers with prompt urticarial rash, slight epistaxis, and the platelet count a few hours later was 50,000. There was no further purpura or bleeding until May 30 when he found a piece of cake within reach, ate it, and once more had moderate epistaxis. Again a slight but suggestive reduction in platelets was noted

over the previous count made on May 22. By June 7 the platelet count had reached 220,000, and subsequently the count has been consistently well over 200,000.

There has been no opportunity for ingestion tests, and deliberate clinical trial with egg has not been considered justified. Elimination of contact with feathers to which there was a positive cutaneous reaction has relieved him of recurrent nasal

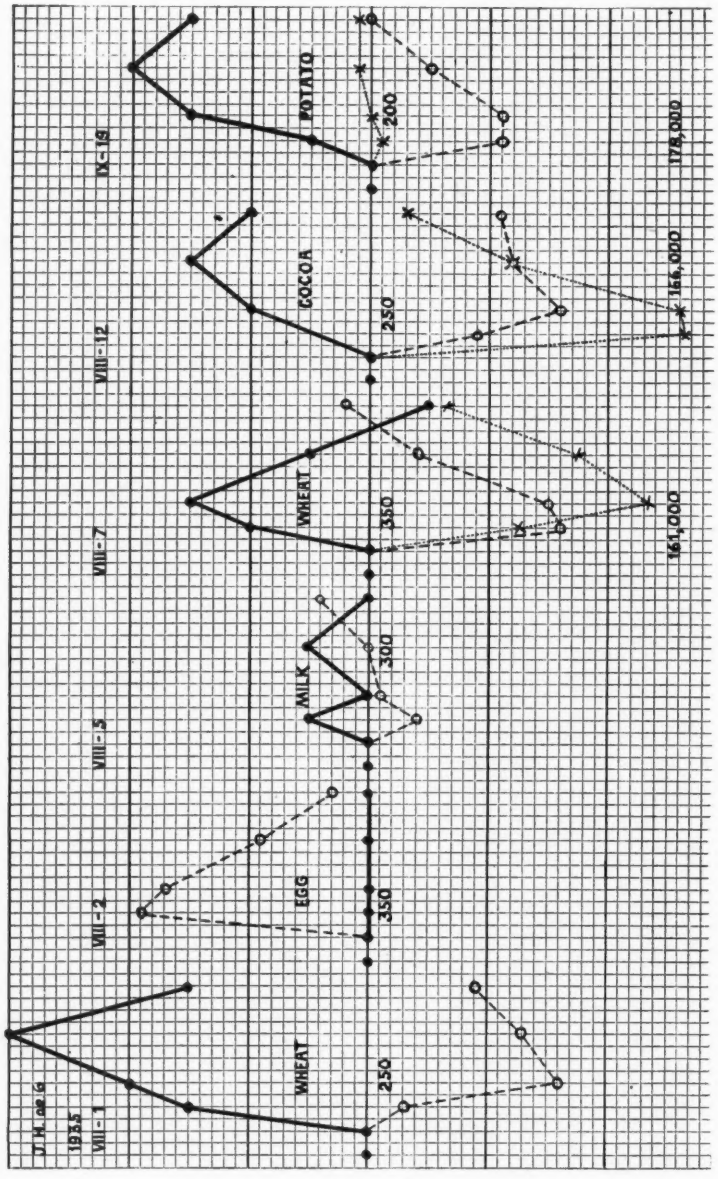

Fig. 3.—Case 4. Positive hematologic response after wheat and cocoa ingestion with associated fall in thrombocyte level. Epistaxis occurred after testing with each. Positive hematologic response after potato ingestion without platelet depression. Negative response to egg and to milk.

stuffiness and an asthmatic cough. For the past eleven months he has remained entirely free from all purpuric manifestations, has gained weight, and is in excellent condition.

CASE 4.—J. H., a schoolboy aged six years, was seen Aug. 1, 1935, with hoarseness present since age two years. One sister has asthma, another sister has had

urticaria and violent asthma following a bee sting. His brother is wheat sensitive; his mother has vasomotor rhinitis, and during each of three pregnancies had purpura and bleeding which disappeared after delivery.

In the winter of 1934, headache and fever followed egg ingestion, and in consequence egg had been eliminated for a year.

About once each month since he was six months old he has had recurrent attacks of epistaxis. An ingestion test with egg was negative on August 2. On August 4, after several weeks of wheat avoidance which had been instituted by the mother, a wheat ingestion test was done and an allergic type of blood response observed. That evening he had nosebleed for the first time in a month. A milk ingestion test on August 5 was negative, and on August 7 wheat ingestion test was repeated with thrombocyte counts which had not been made in the previous test. Thirty minutes after wheat ingestion the thrombocytes had fallen from 161,000 to 114,000,

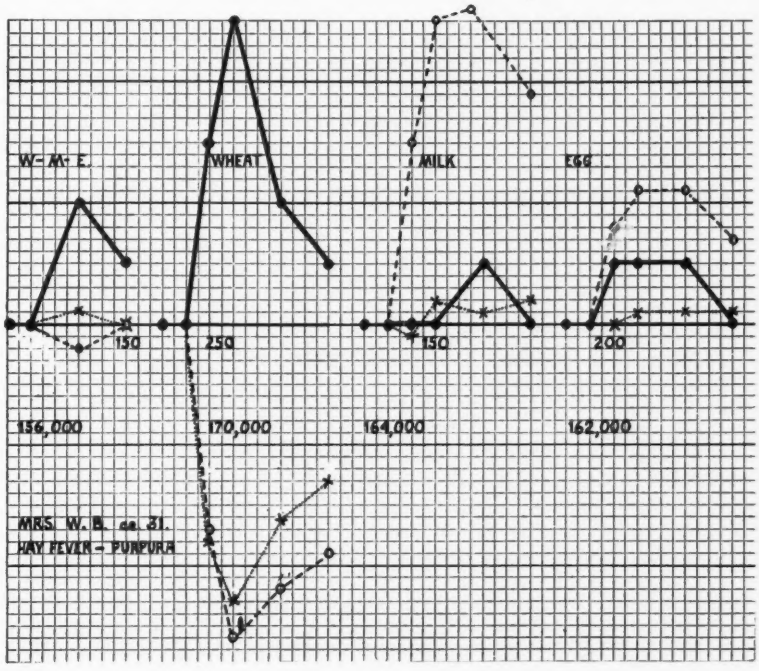

Fig. 4.—Case 5. Suggestive response after combined ingestion of wheat, milk and egg. Positive response with associated depression of thrombocytes after ingestion of wheat. Negative response after milk and egg.

and again epistaxis occurred in the evening (Fig. 3). On August 12 he was tested with cocoa. In addition to leucopenia and eosinophilia, there was a sharp fall in thrombocytes from 165,000 to 113,000 fifteen minutes after ingestion and that evening he had another severe nosebleed.

CASE 5.—Mrs. W. B., aged thirty-one years, was seen in May, 1935, with a history of fall hay fever first observed in 1934. All her life she had bruised easily. Two years before during pregnancy there was bleeding from the gums and repeated mild epistaxis which was not observed subsequent to delivery. In December, 1936, during her second pregnancy the same tendency to bleeding was observed. Hematologic study after wheat ingestion showed leucopenia, eosinophile rise, and a simultaneous fall in thrombocytes from 170,000 to 124,000 (Fig. 4). No significant alteration in thrombocyte level occurred after ingestion of egg or milk, both of which

foods caused normal digestive leucocytosis. Wheat was restricted during the latter months of pregnancy and the tendency to bleeding disappeared. In April, 1936, she had an uneventful delivery.

CASE 6.—Mrs. A. D., aged forty-two years, was seen in November, 1935, complaining of menorrhagia, and extensive black and blue spots on the skin at the menstrual period. Gynecologic examination was essentially negative. Blood findings were normal with a platelet count of 170,000. Egg ingestion was followed in thirty minutes by a fall in leucocytes, moderate rise in eosinophiles, and a fall in the thrombocyte count from 174,000 to 144,000 (Fig. 5). There was no essential change in the thrombocyte level after ingestion of wheat or milk, both of which caused normal digestive leucocytosis.

In each of the first three cases we believe we are justified in believing that purpura and thrombocytopenia were relieved by the elimination of foods. In the first patient return of potato to the diet was followed by

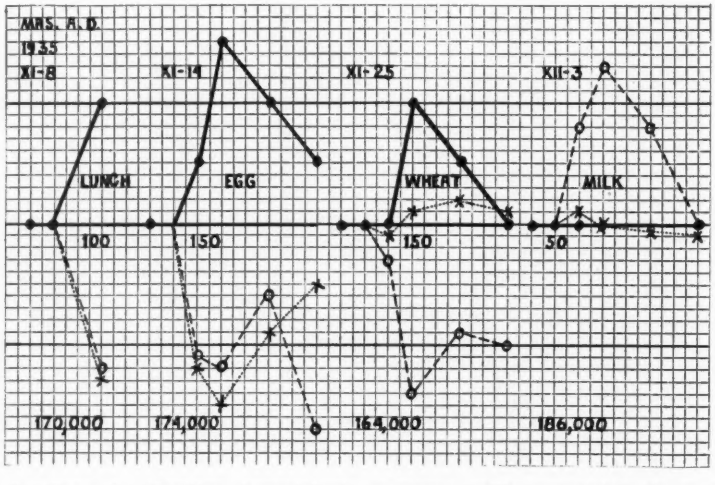

Fig. 5.—Case 6. Positive hematologic response with associated depression of thrombocytes after mixed meal, and after egg ingestion. Positive response after wheat ingestion, but without thrombocyte depression. Negative response to milk.

moderate reduction in the thrombocyte level, increase in subcutaneous bleeding, headache and abdominal distress. Subsequently an ingestion test with potato showed a temporary reduction in thrombocytes associated with leucopenia and eosinophilia. This we believe furnishes additional suggestive evidence that thrombocytopenia may be one phase of an allergic food reaction.

In the second patient prompt clinical improvement and thrombocyte increase followed milk and potato elimination, both of which foods caused distress and thrombocyte depression on ingestion tests.

In the third patient bleeding and thrombocyte depression recurred on two occasions after eating wheat, and diet restricted to nonreacting foods was followed by cessation of bleeding and rise in thrombocytes to the normal level.

We believe it to be a reasonable hypothesis that the same underlying allergic mechanism may be responsible for thrombocytopenic purpura, as well as for the recognized anaphylactoid type (Schoenlein-Henoch). In the anaphylactoid type of purpura increased capillary permeability is present alone or is the predominant manifestation, while in thrombocytopenic purpura profound depression of thrombocytes also occurs as a part of the allergic response, and is comparable to the leucopenia observed in granulocytopenia after the ingestion of amidopyrine[5] and similar drugs by specifically hypersensitive persons. Milder thrombocytopenic reactions corresponding to the leucopenic response observed after ingestion of allergenic foods[6] should occur if the hypothesis is correct, and the last three cases illustrate mild or subclinic hemorrhagic reactions observed in patients with normal or slightly lowered platelet counts. In each of these patients it was possible to demonstrate a definite fall in thrombocyte level after ingestion of one or more test foods which occurred simultaneously with the maximum fall in leucocytes. In each instance those foods which caused normal digestive leucocytosis also caused no significant alteration in the thrombocyte level.

DISCUSSION

In patients with essential thrombocytopenic purpura elimination of specific foods was followed by marked clinical improvement and return of a normal blood picture. Furthermore, ingestion of certain specific foods by these patients was followed by recurrence of bleeding and a suggestive lowering of the thrombocyte count.

In two of these patients temporary depression of the thrombocytes was observed thirty minutes after ingestion of some, but not all foods which caused a leucopenic response and associated eosinophile rise. This depression of thrombocytes occurred coincident with the maximum depression of leucocytes and rise of eosinophiles, and was not observed after ingestion of foods which caused normal digestive leucocytosis.

A similar thrombocyte depression after ingestion of specific foods was observed also in a group of three patients with unexplained bruising and hemorrhagic tendencies in whom the blood pictures were essentially normal. In one of these patients epistaxis occurred in the evening on three occasions after ingestion of a food which had caused transitory depression of the thrombocyte count.

The evidence demonstrating that thrombocytopenic purpura may result from drug allergy is most convincing. It is generally accepted that allergic reactions to foods may be responsible for alterations in capillary permeability and we believe our observations indicate that a similar allergic response to foods may depress the thrombocyte level sufficiently in certain cases to produce typical essential thrombocytopenic purpura.

It is our conception that thrombocytopenic purpura and anaphylactoid purpura both result from an allergic reaction. In anaphylactoid pur-

pura increased capillary permeability is the predominant or only hematologic manifestation; in thrombocytopenic purpura profound depression of the level of circulating thrombocytes with its associated effect on bleeding time and clot retractility is added.

We wish to emphasize that we regard food allergy as only one of many possible etiologic agents in thrombocytopenic purpura. We are convinced, however, of its importance and believe that an allergic investigation of patients with this disease offers a far more hopeful therapeutic approach than do the empiric and nonspecific methods of treatment so universally employed at the present time.

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DISCUSSION

DR. FRED W. GAARDE, Rochester, Minn.—I should like to ask how many patients besides these three were observed. It is difficult to draw conclusions from three cases in a disease which is subject to remissions and periods of improvement such as thrombocytopenia.

We now have a large series of patients with hemorrhagic purpura who apparently have been completely cured, the blood having returned to normal, by the surgical procedure of splenectomy. A few of these patients have had remissions, but the majority seem to remain well. It is very difficult to account for the results obtained by splenectomy on a basis of food sensitiveness being the cause of the purpura. If food sensitiveness is a factor in this disease, most certainly an intensive study is indicated as to the relationship between the spleen and the allergic phenomena.

DR. MILTON B. COHEN, Cleveland.—I do not know anything about thrombocytopenic purpura, but I am sure any one who has observed any large group of allergic persons will have found that a large percentage of them bruise easily.

Those who bruise easily represent perhaps 10 or 15 per cent of people, although I have not made any attempt to count them accurately. They do not have any bleeding, but they do bruise easily.

I should like to ask Dr. Squier whether he thinks that bruising of this type may be related to the thrombocytopenic picture, or whether that is the type of thing he was classifying under change in capillary permeability.

DR. SAMUEL M. FEINBERG, Chicago.—I think this is a very nice piece of work; however I think the title of the paper leads one to believe that it is a discussion of the thrombocytopenic response to food allergy in general, just as the leucopenic response is a general response to food allergy.

I believe it would be very much better, when the paper comes to publication, not to create confusion, to entitle it "Thrombocytopenic Hemorrhage Due to Specific Foods."

DR. BEN Z. RAPPAPORT, Chicago.—I can add one more patient to the list that Dr. Squier speaks of, a physician, who had thrombocytopenic purpura for at least five years. He is very definitely sensitive to a number of foods, especially onions, almonds, and the cabbage family. On elimination of these foods to which he gave very definite skin reactions, his attacks of purpura, and his hemorrhages, as well as bullous lesions of the mouth that became hemorrhagic, have disappeared. As long as he maintains the diet he has no symptoms. When he eats any of the foods to which he gave reactions, he has attacks of purpura.

I have had several other patients who have not shown any changes in the thrombocytes, but who had severe hemorrhages from the nose, from the rectum, and from the vagina, on the ingestion of definite foods to which they have not given definite skin reaction, in one case particularly, sensitive to coffee.

DR. C. B. BOHNER, Indianapolis.—I have one case to report in which scratch tests showed not more than one-plus reactions; ten of them were done, but these gave marked clinical symptoms within thirty minutes.

Dr. Squier's and Dr. Madison's paper emphasizes that reactions occur from the ingestion of foods given as therapeutic tests. It would seem that one would have to be very careful in testing these individuals by either skin tests or food ingestion for fear of dangerous reactions.

DR. NARCISSE F. THIBERGE, New Orleans.—I wish to say a word on the control of purpura. We have an allergic service at the Charity Hospital to which the medical division refers many cases of purpura for testing; the hemorrhages were found due to food allergy and pollen allergy in various forms, but the picture was never uniform.

Without exaggeration, we estimate that during the last ten years 100 such cases were tested for the men in charge of the medical service; we could control these patients very well with injections of histamine. We found it difficult to restrict the very poor to any special diet, and as a short cut we have applied histamine.

The result was sufficiently satisfactory and spectacular to induce the man in charge of the medical cases also to use histamine in the services, and it is only very seldom now that the patients are referred to us for preliminary testing.

There is one point I want to make clear. The form of purpura was not identified in each case, as these cases belong to other services; hence we are not prepared to say that each of the estimated 100 cases was thrombocytopenic.

DR. SQUIER.—If by eliminating reacting foods from the diet splenectomy can be avoided, a great deal has been accomplished in the management of thrombocytopenic purpura. This approach avoids an exceedingly dangerous operation.

Dr. Cohen, I feel that many allergens may cause both platelet depression and increased capillary permeability. We have observed one very interesting patient who had severe menorrhagia during the course of pollen therapy for ragweed hay fever. After her pollen dosage reached about 1,200 units, she began to have severe menorrhagia. She was referred to a gynecologist, with negative findings. As soon as the fall pollen season was over, the menorrhagia ceased. Although she was convinced that the excessive bleeding was due entirely to the pollen therapy, she returned the next year for pollen treatment. Again during her treatment there was marked increase in menstrual flow. Thrombocyte, eosinophile, and leucocyte counts were made before and thirty minutes after the injection of pollen, and she was found to have a definite drop in thrombocytes and leucocytes and a rise in eosinophiles after the pollen injection.

This year she is being studied with counts before and after each pollen injection. Thus far she has had only two injections, and no alteration in any of the blood elements was observed.

I was very much interested to hear the report Dr. Rappaport gave of his additional cases. In thrombocytopenic purpura as in other allergic conditions nonspecific measures apparently have a beneficial effect. The control of thrombocytopenic purpura by histamine injections falls in this category. I feel that our attempt should be to find and eliminate the specific factors rather than resort to nonspecific measures.

I am perfectly willing to have the title changed, Dr. Feinberg.

LIPIDS OF THE BLOOD PLASMA IN HAY FEVER AND ASTHMA*

STEARNS S. BULLEN, M.D., AND WALTER R. BLOOR, PH.D.
ROCHESTER, N. Y.

IN 1933, Hansen[1] presented some studies which indicated that the serum of infants suffering from eczema contained fatty acids which were less unsaturated than those of normal controls. He found that the eczema improved when the infants were fed oils especially rich in unsaturated fatty acids and at the same time the iodine number in the serum rose to normal.

Because some cases of infantile eczema are atopic in origin, and the majority of cases of asthma and hay fever are manifestations of atopy, it seemed worth while to study the lipids of the blood plasma in a group of patients suffering from these diseases. This seemed especially desirable, because some pharmaceutical houses have recently put on the market oils, rich in unsaturated fatty acids, for which their advertisements make unwarranted claims as to the prevention and cure of asthma and hay fever as well as eczema.† Furthermore, so far as we can learn, no similar studies have been published.

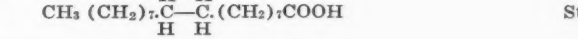
The blood samples were obtained from 14 patients ranging in age from twenty-four to sixty years, who had the seasonal or perennial types of hay fever, or asthma, or both, and one who in addition had had eczema from infancy. Specific hypersensitiveness could be demonstrated, by means of skin tests, on all except three. As controls, blood from 12 non-sensitive individuals in the same age range was studied. The blood was collected about three hours after breakfast. The studies were made in

Read before the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 2, 1936.

*From the Department of Medicine and the Department of Biochemistry, School of Medicine and Dentistry, University of Rochester, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals.

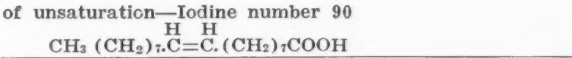
†The following are formulas, showing varying degrees of unsaturation, of the more frequently occurring types of fatty acids.

Saturated—No iodine number.



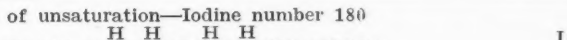
Stearic Acid

One degree of unsaturation—Iodine number 90



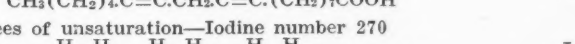
Oleic Acid

Two degrees of unsaturation—Iodine number 180



Linoleic Acid

Three degrees of unsaturation—Iodine number 270



Linolenic Acid

These last two are the so-called "essential" fatty acids.

The functions of the unsaturated fatty acids are not well known except that they are essential for growth and maintenance as recently shown by Burr.

June, at which time the patients who were sensitive to the grass pollens had hay fever while those sensitive to ragweed pollen did not.

Determinations of the total fatty acids, the cholesterol fatty acids and the iodine number were made by the methods in use in this laboratory. The results are shown in Table I.

TABLE I

DISEASE	SENSITIVE TO	TOTAL FATTY ACIDS MG. PER 100 C.C. PLASMA	CHOLESTEROL	IODINE NUMBER
Asthma—Hay fever	Ragweed pollen	308	208	97
Hay fever	Grass pollens	261	160	112
Hay fever	Grass pollens—Ragweed pollen	266	160	93
Asthma—Eczema	Ragweed pollen—Silk	370	280	100
Asthma—Hay fever	Ragweed pollen	468	207	94
Asthma—Hay fever	Ragweed pollen	294	124	96
Asthma—Hay fever	Ragweed pollen—Cat and dog dander	348	140	78
Asthma—Hay fever	Grass pollens—Ragweed pollen	190	60	90
Hay fever	Ragweed pollen	383	137	73
Hay fever	Ragweed pollen	341	126	-
Asthma	House dust	174	171	75
Asthma	-	510	160	97
Vasomotor rhinitis	-	439	92	-
Asthma	-	200	107	83
	Average	325	152	91
	NORMAL CONTROLS			
		417	195	108
		361	134	68
		315	167	110
		432	235	88
		259	175	100
		245	175	106
		562	195	85
		257	175	98
		275	120	100
		400	156	95
		255	110	88
		235	110	96
	Average	334	162	95

In both groups there are the usual variations from person to person. The averages of the results, however, are so nearly identical in the two groups that the slight differences seem to have no significance.

CONCLUSION

So far as these results show, there is no definite difference in the degree of unsaturation of the plasma fatty acids between adults suffering from asthma and hay fever and those who do not have these diseases.

Therefore it could not be expected that the feeding of unsaturated fats would be of therapeutic value in asthma and hay fever.

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DISCUSSION

DR. ROBERT CHOBOT, New York.—I should like to add a word to what Dr. Bullen has said. Not so long ago the same commercial school of thought approached me with the idea of trying not only nonsaturated fatty acids but also a wheat germ oil both in cod liver oil. I was highly skeptical. They were willing to supply a large quantity for a clinic of allergic children, and they were even willing to supply the cod liver oil. I knew the cod liver oil was not going to hurt them. I did not know what the unsaturated fats and wheat germ oil were going to do. These advocates claimed a loss of hypersensitivity as a result of their ingestion.

I agreed, however, taking the precaution not to use the mixture on cottonseed sensitive children. We gave them large quantities of the cod liver oil containing both of these substances. After rather extensive use the only thing that I could ever see was the gain resulting from the use of the cod liver oil. As far as amelioration or the disappearance of any allergic phenomenon or change in the sensitivity, or anything that even the most optimistic advocate could look for, I can add the practical observation to Dr. Bullen's chemical one, that the thing is without use and without any rationale that I could see.

DR. ROYCE PADDOCK, Newark.—It gives us all a sense of satisfaction to realize that work of this kind has been done accurately. I think we have felt some curiosity about many of the chemical constituents of the blood in these cases. I believe this work will settle such a question, in regard to the lipids.

STATUS ASTHMATICUS

Report of Sixteen Cases*

I. S. Kahn, M.D.
San Antonio, Texas

THE patient with status asthmaticus presents a picture of the most abject misery. Dyspnea, orthopnea and cyanosis are intense, and may persist for many hours, or even one or two days, until approaching exhaustion is obvious. During this time, his epinephrine ration of 0.5 c.c. to 1.0 c.c. gradually increasing to the frequency of every one-half to one hour, or even oftener for one, two or several hours, with, at times, an occasional dose of morphia, has reached the point of giving absolutely no, or only the briefest transitory, relief.

In these cases the cough reflex for the time being either is entirely lost, or, if present at all, is totally unproductive and inefficacious. Coughing efforts result only in increasing the respiratory distress. Headache is common, and at times there is some nausea and vomiting. Pallor, sweating and tremor are marked. The pupillary changes present usually depend on the amount of morphia received and the individual sensitivity to this drug. The pulse is rapid, weak and at times irregular. Consciousness may be totally or partially lost.

Physical examination of the chest reveals either the usual numerous râles typical of bronchial asthma, or their presence to a surprisingly limited degree, and no evidences of consolidation or atelectasis can be found. The patients in this report were considered too uncomfortable or too ill to justify radiographic studies to determine positively the presence or absence of these conditions. The blood examination except at times for eosinophilia is essentially normal. The urine frequently contains albumin and casts, and occasionally sugar.

Of eighty-five admissions to the Nix Hospital (San Antonio, Texas) for bronchial asthma ten fall into the category of status asthmaticus, and six others were seen in other hospitals or at home. Patients with severe chronic intractable asthma securing relief by morphia or even by inordinately frequent daily doses of epinephrine are not included in this report.

The general measures I have used in these cases include the usual near-perfect antigen-free room kept at an even temperature. The maintenance of an even low relative humidity is probably a favorable factor, but I have had no personal experience along that line. The patient

*Read before the Twelfth Annual Meeting of the Association for the Study of Allergy, Kansas City, May, 1936.

is placed at once at as complete rest as possible in bed, with the head and shoulders elevated. Talking and unnecessary bodily movements are restricted. Nothing whatever, not even water, is given by mouth unless asked for, as even efforts of swallowing increase the discomfort.

A repetition of the usual 0.5 c.c. to 1.0 c.c. epinephrine dosages given in other portions of the body not hitherto used for this purpose, deep intramuscular injections of epinephrine, massage of epinephrine-treated areas, and changes to other brands of epinephrine have proved themselves unavailing. Unless there are indications of extreme urgency or contraindications later to be described, a single trial subcutaneous dose of epinephrine in the antigen-free room is my usual custom, of course without result in true status asthmaticus. For some reason, in these cases the antispasmodic radical of the epinephrine does not enter the circulating blood as such at all, or fails if and when it does. Increasing the epinephrine dosage to 1.5 c.c. (20 to 25 minims) gave complete relief in two patients with more or less this type of asthma I have described, but not considered sick enough to be placed in this series.

When subcutaneous epinephrine in doses of the usual size has failed, the possibility of the further indication and efficacy of this drug can better and more safely be determined, not by increasing the dose to such high levels but by proceeding at once to its intravenous administration. The usual dose of the ordinary 1:1,000 dilution so given that I have found beneficial is from two to four minims (0.15 c.c. to 0.25 c.c.),[1] using a tuberculin syringe and a 26 gauge needle. However, even if given slowly and in such small doses, this is an extremely shocking measure; terrific pallor, tremor, sweating, headache, heart pounding, and at times nausea and vomiting supervene almost instantly. I have never seen a patient tolerate even four minims without these symptoms. These untoward manifestations can be avoided or reduced, and as satisfactory therapeutic results can be obtained by using the 1:10,000 dilution (1 c.c. to 2.50 c.c.), stopping the administration at the first sign of relief or of epinephrine symptoms.

This measure alone gave, either after the first dose or after one or more repetitions at from five- to ten-minute intervals, decidedly satisfactory relief in six out of eleven cases in which it was tried. Curiously enough, when some degree of relief has once been so secured, it can be completed and easily maintained by the ordinary usual subcutaneous dosages previously unsuccessful, with the first such subcutaneous dose best given one-half hour after the last intravenous administration.

Most of these patients when first seen exhibited either marked cyanosis or pallor, with at times severe headache, and nausea with or without vomiting, and with or without tremor. These symptoms, in the cyanosed cases, are due to the toxemia and partial asphyxiation accompanying the asthmatic state, requiring epinephrine more efficaciously

administered, and in others the pallor may be due to excessive previous epinephrine administration. The differentiation can easily be made by a small trial dose intravenously.

When epinephrine given intravenously fails (producing or increasing epinephrine symptoms without relieving the bronchospasm more than momentarily), I proceed at once to the use of thoroughly mixed anesthesia ether and olive oil in equal parts given by rectum.[2] I have found the best dosage of this mixture in the average adult to be from five to seven ounces, allowing twenty minutes for its administration. Smaller doses, single or repeated, are ineffectual, as a comparatively deep narcosis is required. No preliminary cleansing enema is given. The dose for a child from five to nine years of age, I have found to be from one and one-half to two ounces.

The narcosis so induced is prompt and will last several hours. In four of the ten cases in this series in which I found rectal anesthesia necessary, this measure produced a satisfactory relaxation of the bronchospasm, subsequently completed by two or three doses of epinephrine (of 3 to 4 minims). In five other cases, during the narcosis period relaxation was not complete, and epinephrine in the usual or somewhat smaller doses was necessary. In one instance, 13 doses of epinephrine in a period of nine hours were required during and immediately after the narcosis, to secure profuse expectoration and perfect relaxation.

I have feared to employ any form of oral anesthesia in these patients. In one patient easily and promptly relieved later by rectal ether anesthesia, inhalation of the 1:100 epinephrine several times gave almost instantaneous relief, lasting, however, only two or three minutes, and followed by bronchospasm, if anything more severe than before its use.

Like all workers in allergy, I have dreaded the employment of morphia in these cases. One must not, however, be too categorical on that point. In a recent patient six epinephrine doses used intravenously followed by a deep narcosis from the usual seven ounces of the ether-olive oil given by rectum gave absolutely no relief to the bronchospasm. After the narcosis had lasted two hours, and repeated epinephrine again proved futile, in desperation, morphia, grain one-eighth, was given subcutaneously, and promptly resulted in the first signs of relaxation. This relaxation was made complete by the repetition of the morphia every three or four hours until four more doses had been given.

In this series of sixteen cases, there were no deaths. My only failure to secure a high, almost perfect degree of relief in from six to twelve hours in the very worst cases, occurred in a narcotic addict in whom I feared to give the usual full dose of rectal anesthesia. (The patient was relieved by morphia used intravenously self-administered.)

I have found inefficacious and time wasting the following measures used in early cases of this series—atropine subcutaneously, and iodides,

calcium and sodium amytal (with one near fatality) intravenously. The dehydration present to a marked degree in these cases apparently does no harm, and seems to me to require no specific measures for its correction. I used glucose intravenously and the oxygen tent in three of these cases, but without apparent benefit to the asthmatic state. On a few occasions when some cardiac support seemed necessary, I have used caffeine sodium benzoate, and in one case, coramin. But, on the whole, my impression is that therapeutic manipulations beyond intravenous epinephrine and rectal ether narcosis and possibly morphia are superfluous and of little benefit.

Surgical measures, such as bronchoscopy and intranasal work, in these cases are for the time being impossible. I have had no experience with dorsal sympathectomy.

The convalescence of these desperately ill patients handled in this manner that I suggest, is surprisingly prompt and complete. Twenty-four hours after relaxation has been secured, it is almost impossible to believe that such a comfortable patient could be the same individual who had so recently passed through such a terrific nearly fatal experience.

CONCLUSIONS

1. Sixteen cases of status asthmaticus are reported, all desperately ill patients, and in all of whom hypodermic doses of epinephrine of the usual size often repeated had proved totally inefficacious in relieving the bronchospasm.

2. Of eleven of these patients in whom it was tried, six were relieved by administration of epinephrine intravenously.

3. Of ten of the patients in whom it was tried, four were relieved by rectal anesthesia, using equal parts of ether and olive oil.

4. In the balance, six patients, in addition to the anesthesia, epinephrine subcutaneously was required, being repeated as needed during the narcosis period, and in one of these morphia also was given.

5. Further therapeutic measures were seldom required.

6. There were no deaths. Complete relief was secured with but one failure—a narcotic addict, relieved by morphia intravenously self-administered.

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2. Maytum, C. K.: Bronchial Asthma: Relief of Prolonged Attack by Colonic Administration of Ether, M. Clin. North America 15: 201, 1931.

DISCUSSION

Dr. Alan G. Cazort, Little Rock.—I wish to ask a question; to know if I am safe in a little procedure sometimes used. In three patients considered desperately ill I have followed the ether-oil treatment with

0.07 c.c. of typhoid vaccine intravenously or with 1.5 c.c. subcutaneously, using a dilution of 1,000-million to the cubic centimeter. Is the intravenous treatment safe?

DR. GEORGE L. WALDBOTT, Detroit.—I shall show you a picture of a death, in my exhibit.

DR. CAZORT.—I have used the method and as Dr. Kahn has said, have noted in twenty-four hours a breaking loose of the thick tenacious sputum, but do not know whether the ether or the fever is responsible, or whether there is danger.

DR. GEORGE L. WALDBOTT, Detroit.—I do not wish to discuss Dr. Kahn's method of treatment. We all have our own experience in the handling of these cases, and each one's opinion should be respected.

As far as my own routine is concerned, I am used to taking certain steps in the management of this type of case. First, I attempt to hospitalize the patient if this is at all possible. Removal of the patient from the inhalants specific to him to which he had been exposed for some time either at his own home or in the immediate locality is in itself a very important therapeutic measure. Second, I do not give any drugs as soon as the patient has entered the hospital; particularly do I try to eliminate morphine and other medications which he may have had before. Patients who have been accustomed to taking large doses of ephedrine or epinephrine do particularly well by discontinuance of these drugs, which is often surprisingly easy to accomplish. I feel that this measure alone is often the key for successful treatment.

Third, among the few drugs which I may use are a hypnotic such as sodium amytal in order to induce relaxation. Oxygen, I believe, is indicated in cases with marked cyanosis. However, in a number of patients, this had to be discontinued, because the patients felt too uncomfortable under the oxygen tent. Glucose solutions by hypodermoclysis or intravenous injections may serve the purpose of forcing fluids, aiding the hepatic function and, if used in hypertonic solutions by the intravenous route, to withdraw fluid from the tissue into the blood stream. While glucose may thus aid in the physiologic defense of the system, I have never seen a distinctly alleviating effect on the asthmatic attacks.

If the patient does not improve with the above measures, I use as a fourth resort desensitizing treatments with extremely small doses of whatsoever antigen to which the patient may be sensitive. I frequently administer a highly diluted extract of the pollen which is in the air at that time regardless of whether or not the patient's skin reaction is positive. I believe that pollen is the primary cause in most cases of severe asthma and that skin tests in desperately ill asthmatic persons are frequently negative. I give these injections as often as every three hours, according to the rapid desensitization method previously outlined before this society.

As a fifth measure I may use convalescent serum of patients successfully treated against the pollen which is in the air at that time. I hope to be able to report on this method at a later date. Cooke and his collaborators presented the experimental basis for this treatment last year.

If all these measures should fail, I call in a bronchoscopist. The elimination of mucus and the dilatation of contracted bronchi have repeatedly proved to be a life-saving procedure. We should all be aware of it in an emergency.

In this connection may I say that ether is known to increase the secretion of the mucous glands of the bronchi. In spite of occasional beneficial results with ether narcosis we should remember that obstruction of bronchi by mucus is considered one of the causes of death in asthma.

Dr. Harry L. Huber, Chicago.—Dr. Kahn gave statistics to show that deaths from asthma in one series were 3 out of 70, and in another 6 out of 70. It seems to me that this is a rather high percentage. It is very important to find out what medication was given to these patients. A narcotic, given for relief, is the thing that causes death in most of these cases.

Dr. Francis M. Rackemann, Boston.—I came too late to hear the paper, but I understand nothing has been said about helium in these cases. Now, the patients do die, Dr. Huber. I have seen a number, and the last one only a month ago, and there was no apparent reason why she should die, except that she went from bad to worse until she died.

Dr. Huber.—Yes, that happens.

Dr. Rackemann.—Tomorrow morning, in the Section on Medicine, there will be a paper by Dr. A. L. Barach, on the use of helium oxygen mixtures. I have seen Dr. Barach's laboratory and some of his results, and he tells me that as soon as the patients begin to inhale the helium oxygen mixtures, they become relieved in a very few minutes. The treatment has to be given intermittently for perhaps a day or two, after which the attack will pass and adrenalin will once more become effective.

Dr. B. G. Efron, New Orleans.—I think that if we would use aminophyllin—we have found in 33 per cent of cases that are adrenalin fast, that aminophyllin intravenously will relieve asthma when the adrenalin has failed to relieve it, and I suggest that Dr. Kahn in his next adrenalin fast, give a dose of aminophyllin. About 33 per cent will respond to it.

Last year at the Atlantic City meeting, the effect of various drugs on the skin tests was reported. It was found that only three drugs affected the skin reaction. One was aminophyllin, one was adrenalin, and the third one was ephedrine; adrenalin reducing the skin reaction the greatest amount, aminophyllin next, and ephedrine third.

Dr. G. Piness, Los Angeles.—As far as dust-free or antigen-free rooms are concerned, we do not have one; therefore I am not in a position to discuss their value, but it seems to me that when patients get to the point where they must be removed from their present environment to a hospital they are usually quite ill or have an intractable type of asthma which does not seem to respond to any treatment. Change of environment in many instances, whether it be to a room such as described by Dr. Kahn or simply from one particular environment to another, many times will give immediate relief, but not in the type of patient Dr. Kahn spoke of this morning.

Epinephrine is a drug that we all use and use freely, and in fact many teach their patients to administer to themselves, especially the type of patient Dr. Kahn has described. Such patients are prone to administer the drug at increasingly short intervals as the symptoms persist and eventually find that the only result of this administration is tremor, pallor, and tachycardia. In such instances I should hesitate to give intravenous doses of epinephrine, regardless of the minuteness of the dose or the weakness of the dilution.

It has been our experience in this so-called epinephrine-fast group that the best thing to do is to discontinue its use over as long a period as possible. In order to do this we must find some substitute that is effective, and we have found caffein frequently to answer this need. It is often effective by mouth when given in two to four grain doses of the alkaloid at intervals of two to four hours, or intramuscularly in the form of caffein sodium benzoate at intervals of about four hours. If freedom of symptoms is obtained for a period of twenty-four to seventy-two hours, epinephrine will again give relief of symptoms should they recur.

We now come to the question of pallor and cyanosis in these individuals. To my mind, the latter indicates only one thing and that is bronchial obstruction which is chiefly due to plugging by thick tenacious inspissated mucus. The physical characteristics of this mucus are chiefly due to the result of dehydration which is not uncommon in the sequence of events leading up to the so-called status asthmaticus. Morphine is also a contributing factor in the production of cyanosis because with the administration of morphine the cough reflex upon which the removal of the mucus is dependent is thereby lost. So it is not infrequent to trace directly to morphine the cause of the marked cyanosis of our patients. As regards the pallor in status asthmaticus, I feel that much of it may well be due to a prolonged administration of adrenalin plus exhaustion. In any event the indications are to stop the administration of adrenalin and morphine and to force fluids and potassium iodide, which will tend to thin out the bronchial secretions and permit the patient to relieve his obstruction by cough.

Concerning ether anesthesia, in my early days I gave a great many ether anesthetics and found that the surgeons were all most apprehensive about using ether anesthesia in asthmatic patients. But to their surprise the patient was usually improved following such an anesthetic. Later on I observed that many patients with status asthmaticus who could not be relieved by methods at hand when administered ether as an anesthetic were in many instances relieved of their asthma. One thing I want to leave with us is that the status asthmaticus individual if given mental rest plus fluids will usually come out of his attack in good condition. Chloral hydrate or chlorotone, given per rectum, will give mental rest but must not be given over too long a period of time.

Dr. Robert W. Lamson, Los Angeles.—I agree absolutely with Dr. Piness' statement that after making five or six trials with epinephrine or other drug, and the desired response is not obtained, its use is contraindicated for the time at least.

One might ask, Why such a variety of experiences in treating "asthma"? I believe the answer is that there are many kinds of asthma and they may require different methods of treatment. Palmer (J. A. M. A. **93**: 433, 1929) states: "If a patient in middle life or over, who suffers from paroxysmal attacks of dyspnea is not relieved by morphine, allergic asthma is likely." I do not believe that the failure of morphine or the success of epinephrine to afford relief is pathognomonic. The former drug need not be used in analgesic doses. Smaller amounts, such as $\frac{1}{20}$ gr. (3.3 mg.) may be employed. In this quantity it acts as an expectorant and not as a depressant. When used with 0.25 c.c. to 0.5 c.c. of epinephrine 1:1,000, the results are much better than with either drug alone, and the small amount of opiate does not disturb the patient.

Rarely is it necessary to remain in constant attendance upon the asthmatic patient for fifteen to twenty hours.

A small funnel may be obtained at the ten-cent store, then this fitted to a urethral catheter. Some member of the patient's family can be taught to use this apparatus for the rectal instillation of ether in oil. The addition of chlorbutanol reduces the local irritation and possibly enhances the systemic effect of the ether. I should like to ask Dr. Kahn whether he uses the ether and oil mixture in young children, and how he encourages them to retain it.

DR. MILTON B. COHEN, Cleveland.—It seems to me that we are all talking about the symptom asthma that our patient has and we forget that he is a very sick patient whose status asthmaticus makes him have many things wrong with him besides the asthma which seems to be choking him to death.

Many of the differences of opinion arise from the fact that we have not considered the pathology of what is before us, or the disturbances in physiology during the time the patient has the condition. It takes four or five liters of water every day to keep an individual going, the water he gets in his food, and the water he drinks. The patient in status asthmaticus cannot drink. He cannot swallow anything, and after two or three days he has five or six or seven liters of water deficiency, and the important thing is to provide him with fluid. Giving such a patient five or six intravenous injections daily does not supply nearly enough fluid. If you are going to do anything intravenously in this sort of patient, the best thing is to insert a cannula and run the fluid in minute after minute, hour after hour, and if you decide you want to give epinephrine or caffein, inject it in the tube and you will not have to spend fourteen hours a day putting needles in the patient's veins. The whole thing can be accomplished simply.

DR. C. K. MAYTUM, Rochester, Minn.—Soon after Dr. Barach reported his results with helium and oxygen in severe asthma, we obtained several tanks of it to have on hand. The first patient on whom we tried it was a nurse with as severe an asthma as I have ever seen. Her condition became worse in spite of all types of treatment, and it looked as though she would die if relief were not obtained. Use of the oxygen tent gave absolutely no relief; dyspnea was severe and constant, and cyanosis was extreme and not influenced by oxygen alone. When helium was added, there was almost immediate improvement; respiration became less difficult, cyanosis gradually subsided, and the patient was able to relax and to rest. Epinephrine again became effective, and within a comparatively short time she was able to leave the hospital. Our results with its use in other cases have been quite satisfactory, and I feel that it is a valuable aid in the treatment of the desperately ill asthmatic patient.

Unfortunately, the cost is high and technical difficulties in administration limit its use considerably. It is possible that in the near future the government may make it available for therapeutic purposes at a more reasonable cost.

DR. M. MURRAY PESHKIN, New York.—It is apparent that in the handling of a patient with status asthmaticus an allergist has first of all to be a physician.

We have heard today and in the past few years, words of caution against the use of morphine. Some allergists advocate that morphine

should never be used in patients with asthma. I have become so conscious of the ill effects from morphine reported by various workers that I have been obliged to recognize the potential danger of this drug in status asthmaticus by avoiding its use as much as possible, although my former experiences did not justify such a course. It is conceded that morphine should not be employed in any case of asthma when adrenalin can control the situation. However, the appropriate application of morphine in patients with status asthmaticus based on my experiences with it in the last two years, has compelled me to employ this drug with less hesitation.

It can be stated that very few practitioners use morphine without atropine, probably because of an hereditary empiricism. Experience has indicated that atropine does more harm than any possible good to a patient with status asthmaticus.

The use of morphine in repeated doses can do and does a tremendous amount of harm, and here one heartily concurs with Dr. Huber's statement that patients do not die of status asthmaticus so much as from what has been done to them.

I should like to cite a few interesting experiences with patients suffering from severe status asthmaticus. Several years ago a woman was under treatment for asthma. One day she complained of a dryness of the throat. A bland mineral oil solution was sprayed in her throat after which she promptly developed a violent asthmatic attack. She quickly became cyanosed and soon was almost pulseless. Four minims of epinephrine hydrochloride (1:1,000) properly diluted were injected intravenously. This dose was repeated within five minutes but to no avail. The presenting condition became really desperate. Morphine sulphate, ¼ gr. (without atropine), was injected subcutaneously. Five minutes later the attack was completely controlled. This experience made a deep impression, since a fatal issue appeared imminent.

Recently I was called to see a girl, sixteen years of age, who had been in a condition of status asthmaticus for seventy-two hours. She had been given all kinds of therapy except morphine. I administered epinephrine hydrochloride (1:1,000) intravenously on four separate occasions over a period of two hours without inducing the slightest relief. Finally, only one dose of $\frac{1}{20}$ gr. of dilaudid was injected subcutaneously. Within one-half hour the patient sat up in an erect position for the first time in three days. The status asthmaticus was controlled, and the patient reverted to a mild state of asthma readily relieved by small doses of adrenalin.

I believe that the appropriate use of morphine, preferably dilaudid, principally because the latter drug is not combined with atropine, is an effective if not a life-saving measure in some cases of status asthmaticus.

DR. KAHN.—I have had no experience in cases with helium, typhoid vaccine, continuous intravenous fluid administration, aminophyllin, chloral or chloretone. It is possible that a certain number of my cases would have cleared in an antigen-free room without such active treatment measures as I have mentioned, but some patients would have endured hours or days of unnecessary suffering. Dr. Rackemann told me yesterday that at the Massachusetts General Hospital about three cases of asthma a year prove fatal. I feel certain that one or more of the cases in this series of mine without vigorous measures, would have fallen into this category. Reference to the early paragraphs of this paper shows

this to be plausible in the type of case under discussion—the severest form of status asthmaticus. In three cases the oxygen tent was of no help.

Answering Dr. Lamson, I have never used rectal anesthesia on a baby. My youngest patient was seven years old. This procedure, while valuable, is not infallible and will often have to be followed by the measures I have described.

I was glad to hear Dr. Peshkin's remark that morphia is at times useful in these cases. This drug cleared one of my cases beautifully after every other measure I had tried had failed.

Regarding epinephrine used intravenously, Drs. Cohn, Piness and Lamson are absolutely incorrect in stating that pallor, tremor and previous frequently used large doses of epinephrine are contraindications to further use of this drug. They are correct so far as further subcutaneous administration is concerned, but these symptoms, in my experience, are not a bar to the intravenous administration, and I feel that I have saved life in this manner in several cases. My figures show six of eleven patients relieved by this measure alone. It does no harm. The administration should be stopped with the onset of retching with or without vomiting.

THE INTELLIGENCE RATING OF THE ALLERGIC CHILD

GEORGE PINESS, M.D., HYMAN MILLER, M.D., AND
ELLEN B. SULLIVAN, PH.D.
LOS ANGELES, CALIF.

THE precocity of chronically ill children has always aroused sympathetic interest. Handicapped individuals who maintain their places or even surge ahead in the social and economic struggle are universally admired and set conspicuously aside; so conspicuously in fact that the relationship between their handicaps and their superior mental abilities is likely to be identified as one of cause and effect. We are therefore led to speculate on such famous examples as Beethoven's deafness in relationship to his greatness as a composer; on Keats' tuberculosis and his genius as a poet; and on Ambrose Bierce's asthma and his talents as a writer. Such speculations led to the compiling of lists of the great who were fellow sufferers with Bierce, as though such lists might confirm the wishful thinking of those of us who compile them. Add to such evidence the well-known precocity of the chronically ill child, in which group the allergic naturally falls, and but little more is needed to convince us that superior mental traits embellish the allergic constitution.

Balyeat[1] in 1929 was the first to attempt to congeal such speculation into scientifically demonstrable fact. Basing his conclusions on the results of the Otis self-administering test done on 80 allergic and 80 nonallergic children, he concluded that most allergic children are far above normal in mental activity. This conclusion has been the subject of editorial comment in the *Journal of the American Medical Association*[2] and has been perpetuated in several articles and texts dealing with allergy. A critical appraisal of Balyeat's work left us with the desire to repeat it on a more complete and therefore perhaps on a more accurate plan, and the following study is the result.

The allergic children used in this study were from among those attending the Allergy Clinic of the Los Angeles Children's Hospital. They were drawn from all charitable social agencies in the city, for at the time of this survey this was the only complete children's allergy clinic in Los Angeles. Any child under twelve years of age with the proper financial qualifications as determined by the Social Service Department was eligible to the clinic.

The members of the group studied were all active cases attending the clinic once or twice a week regularly for treatment of some allergic ailment. The criteria used for arriving at the diagnosis of the allergic

constitution were based on the family and personal histories, the physical and laboratory findings, the skin tests, and the response to specific treatment. Every case in active attendance at the clinic during the period of the survey was included, omitting only those children under five years of age. The actual testing and correlation of data were done by Ellen B. Sullivan, Ph.D., and Gertrude MacQueen, M.A., of the Department of Psychology of the University of California at Los Angeles. The conclusions are concurred in by all the authors.

The age range of cases studied by us was from 5 years, 5 months, to 15 years, 4 months, the median age being 8 years, 11 months. Fifty per cent of the cases fell between the age of 7 years, 4.5 months, and 10 years, 10 months. Seventeen cases above 12 years (the upper age limit for hospital treatment) were continued for study. Table I shows the distribution of ages in the group.

TABLE I

CHRONOLOGIC AGES OF ALLERGIC CHILDREN STUDIED

AGE	NUMBER OF CASES
15-15:11	1
14-14:11	1
13-13:11	7
12-12:11	8
11-11:11	16
10-10:11	18
9- 9:11	19
8- 8:11	24
7- 7:11	23
6- 6:11	23
5- 5:11	5
Total	145

Median age, 8 years, 11 months.

Each child was given two or more psychological tests. The following number of tests were administered: Stanford-Binet—given to 45 children at random from a total of 145. Goodenough Drawing—given to all children above eight years, except those who could not read or react properly to the test. Detroit Primary Intelligence—given to children under 8 and to those who could not do the National Intelligence Test because of reading or other disability.

TABLE II

DIFFERENCE OF I.Q. MEDIANS WITH DIFFERENT TESTS USED

TEST USED	MEDIAN I.Q.	NUMBER OF CASES
Stanford-Binet	103	45
Goodenough Drawing	100	104
Detroit Primary	103	44
National Intelligence	110	61
Average of three tests	104	145

The different tests used to measure the intelligence levels of the allergic group gave approximately the same result except for the National Intelligence Test which showed a higher median I.Q. This, however, was due to the selection of children to whom this test was given. No child above 8 years who could not read was included in this group, thus eliminating along with children having a reading disability those of low I.Q.'s. Table II shows the difference in median I.Q.'s with the different tests.

TABLE III

INTELLIGENCE QUOTIENTS OF ALLERGY GROUP, EPILEPTIC GROUP, AND A NORMAL SIX-YEAR SCHOOL CONTROL GROUP

INTELLIGENCE QUOTIENTS	ALLERGIC GROUPS		LOS ANGELES CITY SCHOOLS	EPILEPTIC
	STANFORD-BINET I.Q. PERCENTAGE	AVERAGE OF 3 I.Q.'S PERCENTAGE	GROUP I.Q. GROUP TESTS PERCENTAGE	GROUP I.Q. STANFORD-BINET PERCENTAGE
140+	0.0	0.6	1.2	0.9
130-139	4.4	5.5	3.3	1.9
120-129	8.8	12.4	10.2	6.8
110-119	18.0	15.1	21.8	9.7
100-109	26.6	27.5	27.3	19.4
90- 99	35.5	22.7	20.6	17.4
80- 89	6.6	13.7	10.6	19.4
70- 79	0.0	1.3	3.8	5.8
Below 70	0.0	0.6	1.3	18.4
No. of cases	45	145	63,114[3]	103
Median	103	104.1	105	92.4
Quartile deviation	8.9	8.8	11.0	22.3
Range of I.Q.'s	81-139	63-146	Not reported in detail (Inferior to superior)	11-141
Range of age	5:10-12:6	6:7-13:8	Ages covered by normal six-year school (Approx. 6 to 13 or 14)	2-14

The results reported in Table III and Fig. 1 show the distribution of intelligence in the allergy group and offer a comparison of this group with a similar group of unselected children in the Los Angeles City Schools. They also show the distribution of intelligence in an epileptic group in the Children's Hospital.[4]

The test results indicate that the allergy group is not retarded intellectually as compared with the control group. The slight difference in medians of the city school group and the allergy groups cannot be considered significant. The results also show that the children in the allergy group vary in intelligence from inferior to very superior, as also does the control group. There is a slightly smaller number of inferior in the allergy group than in the city school group.

Comparing the allergy group with the epileptic group of similar selection except for condition of illness we find a great difference. The epileptic group is generally very much lower and has a cumulation of cases at the inferior and feebleminded level. The epileptic group also includes the superior levels of intelligence but in smaller numbers.

Balyeat stated in his report that children with allergy "passed their grades with ease even though out of school from one-third to one-half of the time." He presented no data on progress through the grades of children with allergy. Table IV gives the picture of school success as

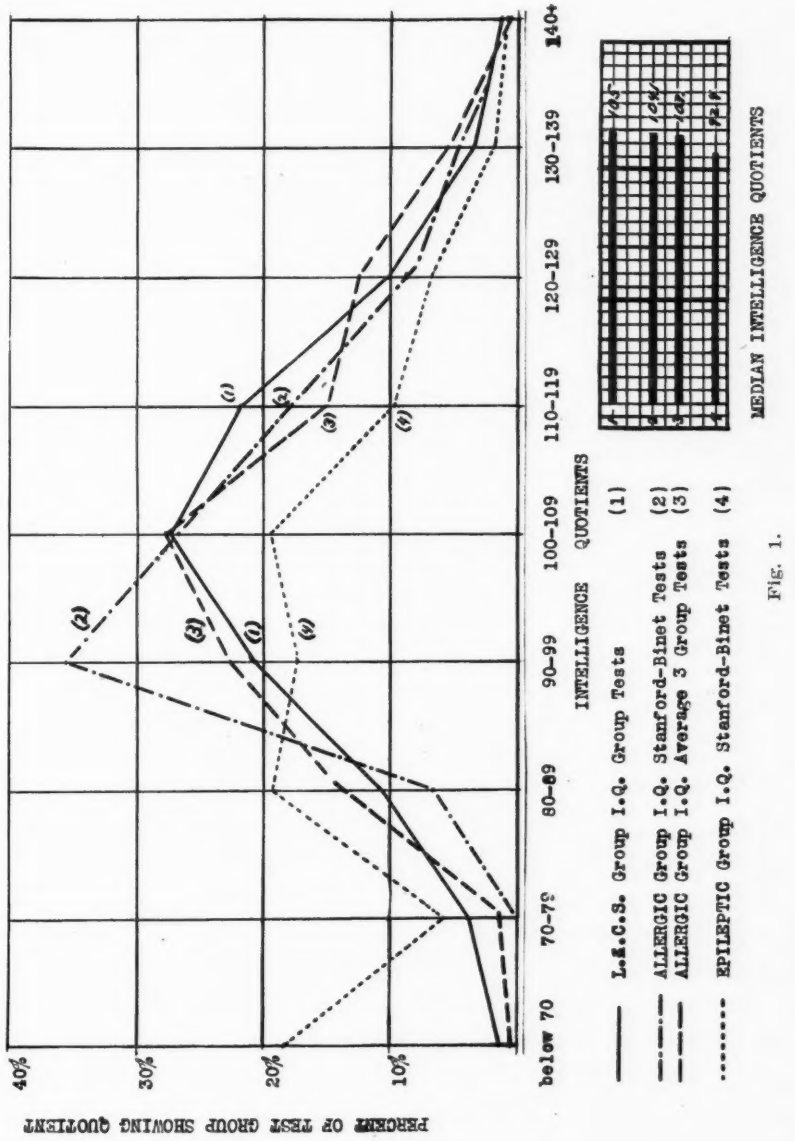

Fig. 1.

measured by grade placement of 100 children for whom this information was available. The group as a whole is neither accelerated nor retarded. The distribution does show 22 per cent retarded one year or more, and only 11 per cent accelerated one year or more. Also the degree of retardation is slightly greater than the acceleration. However,

the illness and discomfort from the disease do not seem to have hampered the children in school in as great numbers to the degree that might be expected from other forms of illness.

TABLE IV

SCHOOL SUCCESS AS MEASURED BY GRADE PLACEMENT OF ALLERGIC CHILDREN STUDIED

SCHOOL STATUS OF VARIOUS GROUPS	PERCENTAGE OF CASES
Accelerated more than two years	0
Accelerated two years	3
Accelerated one year	8
Normal school placement for age	67
Retarded one year	18
Retarded two years	3
Retarded three years	1
Retarded more than three years	0
	100

In order to discover any special abilities or disabilities characteristic of the allergic group, the failures and successes on individual items below or above the general mental level of the individual were tabulated and analyzed. Since failures one year below or successes one year above the general mental level could not be considered important, we summarized only variations of two years.

The allergic group divided itself into four groups (70 Stanford-Binets): Fifty-seven of the 70 children did tests more than two years above their mental age level. Thirty-five of the 57 who did tests more than one year above their general mental level did not fail tests more than one year below their general mental level. Twenty-two of the 57 children who passed tests more than one year above their general mental level, also missed tests more than one year below their general mental level. Nine children failed tests more than one year below their general level and did not pass tests more than one year above their general level. Four children neither passed tests more than one year above nor failed tests more than one year below their general level. The narrow range was characteristic of very few children. A correlation (Pearson Product Moment) between range of tests passed and intelligence was found to be $\pm .349$ with a standard deviation of .010. This shows some positive relationship between wide range and intelligence level.

A comparison of the types of tests passed with the types of tests failed did not show particular traits in which the group as a whole were poor or in which they had exceptional ability. In both failures and successes verbal abilities, memory for different types of material, informational items, mathematical material, drawing designs skill, etc., were represented. The group did not seem to be distinguishable in mental traits as an allergy group from a normal group.

This group of 70 included 15 cases in addition to the original 45 non-selected cases. Because these 15 were selected to be tested because recognized as superior, the greater preponderance of successes above age level in the 70 Binets analyzed cannot be considered significant.

One phase of this study that should be followed up resulted from an attempt to secure comparative information from the state hospitals for the mentally retarded in California. We requested from the two hospitals (Sonoma State Home and Pacific Colony, housing at this time 716 and 2,555 patients respectively), information relative to the incidence of the allergies in their groups. Although the information was not available in statistical form, the following statement from Sonoma gives an indication that there may be found less of the allergy in the feebleminded group than in the normal group. Dr. F. O. Butler, Medical Superintendent of the Sonoma State Home, stated in a letter regarding this matter: "In discussing with our staff this situation, we find that we have but very few with asthma and eczema. However, to answer your letter in detail it would mean a complete survey of our 2,555 cases, which would of course take considerable time and we feel that we have so few that it would hardly be worth while, but we are sure there are no oustanding cases in the institution. We do believe, however, that of the cases we have in these conditions, allergic eczema would predominate far over those with asthma." The reply from Pacific Colony gave similar results.

CONCLUSIONS

1. Children with asthma are very similar in intellectual level to a normal group with the variations of a normal group. They include children of superior, average, normal, and inferior intelligence.

2. There might be some indication that the incidence of allergy is less in the feebleminded group, but the data available are very general and not statistically reliable.

3. As far as school success is concerned, the allergy group is similar in grade placement to the normal group.

4. There is evidence in the allergic group of slightly more school retardation than should be expected if their illness had not handicapped them.

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DISCUSSION

DR. SAMUEL M. FEINBERG, Chicago.—I think many of us are unwilling, or rather do not like, to believe what Dr. Piness has to say, those of us, especially, who are allergic ourselves.

I fall in with Dr. Piness in what he said about his data, but I do not agree with his conclusions. In the first place, he has a group of clinic children, admittedly of lower intelligence and with great handicaps of one type or another, and he compares them with a general group of school children in whom there are probably many who have a great many more advantages and that comparison I believe is unfair. I think it would be just a bit more fair to compare a clinic group of allergic children with another clinic group of another type of children, let us say other types of ailments, such as chronic heart disease, and so forth; or ordinary school children of the average public school with all children of that school who are allergic. If Dr. Piness had compared the patients in his own practice with public school children, his results might have been different.

DR. C. ULYSSES MOORE, Portland, Ore.—Dr. Piness mentioned chronologic ages of these children, and I wonder whether he is going to compare or has compared their bone ages. In the group with lower intelligence quotients, were the carpal bones x-rayed? If so, did their intelligence quotients correlate more closely with their bone ages or their chronologic ages?

DR. MILTON B. COHEN, Cleveland.—Before leaving Cleveland for this meeting, I discussed this problem with Dr. Todd, who has records of repeated measurements of the mentality of some 2,000 allergic children. He has not as yet compared this group with the normals of his series; so I cannot make a definite statement as to the relative differences in I.Q. between these children and normal children. However, comparative estimations in the same children over long periods of time do show that during the stage of active allergic symptoms, the mentality is clouded and mental growth, like physical growth, is retarded. When the allergy is masked, mental growth is resumed and is often accelerated; so that at the time any one observation is made, there may be no evidence of any change from average.

DR. PINESS.—In reply to Dr. Feinberg, I do not think his discussion is fair because, after all, our clinic patients are quite comparable with those one sees in private practice in that our average clinic child compares favorably with the group of children from the public schools who were used as controls. If one takes a cross-section of office patients and compares it with the clinic children, I do not believe there is much difference so far as background and mental status are concerned. As far as bone age is concerned, we did nothing about this in our study, knowing that Dr. T. Wingate Todd is presently carrying on this work and has already published something on it. Our problem is quite different from Dr. Todd's. Dr. Cohen's discussion in which he indicates that there was a clouding of mentality during an attack is in accord with our own observation, but our studies were made when the children were at their best physically and mentally. Children who have acute attacks do not come to the clinic during such periods. So I believe on the whole the results as we reported them today are fair because the figures were not arrived at by us nor did we do the testing nor was any attempt made to influence Dr. Sullivan in the conclusions that she drew as noted in our paper.

EVALUATION OF THE RAGWEED HAY FEVER RESORT AREAS OF NORTH AMERICA*

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THE ragweed pollen hazard is a public health problem and has, at least in its effect, been so recognized by the medical profession in America for seventy-five years. A full appreciation of the problem has come only since the development of desensitization treatment has pointed the need and furnished the funds for quantitative research on the production and distribution of pollen. Doubtless the high degree of success with such treatment has dulled rather than sharpened the interest of most physicians in their scrutiny of places which have been supposed to be more or less exempt from air-borne pollen; they have had less and less need for "absent treatment" for hay fever patients.

Dr. Morrill Wyman, professor of medicine at Harvard University and himself a hay fever sufferer, spent a great deal of effort in the 60's in sifting and tabulating the evidence for and against the localities which were then supposed to be favorable for hay fever sufferers. Of the difficulties of his problem he says:[1]

"In investigating these relations (geographical) it is obvious that the number of facts should be large, while it is equally obvious that the small number, comparatively, of persons liable to the disease, adds greatly to the difficulty of obtaining these facts; for none others than sufferers are competent witnesses, and these for only about one month in the year; none others are *catarrhoscopic.*"

His conclusions were based on the data furnished by 110 "catarrhoscopic" persons.

Dr. Wyman's crude trial-and-error method was excusable in his day and for one who could not bring himself to believe in the ridiculously simple pollen etiology of the disease; but it seems incredible that from that time until the publication last year of my initial atmospheric pollen studies in the resort areas,[2] the uncertain and often dwindling merits of such places as the White Mountains and the upper Great Lakes areas should be judged almost wholly by personal testimonials, colored folders, and radio propaganda. Even the absence of ragweeds in a given region cannot now be accepted as proof of the virtues of that region as an

From the Biological Laboratories of Abbott Laboratories.
*Read before the Section on Preventive and Industrial Medicine and Public Health of the American Medical Association, May 14, 1936.

TABLE I

RAGWEED POLLEN INCIDENCE IN NORTH AMERICA

	PLACE	AVERAGE NUMBER OF HAY FEVER DAYS PER SEASON	MAXIMUM ATMOSPHERIC CONTAMINATION	AVERAGE SEASONAL TOTAL	RAGWEED POLLEN INDEX
Alabama:	Mobile	4	170	462	8
Arizona:	Phoenix	0	10	145	1
Arkansas:	Little Rock	24	363	2171	38
California:	Los Angeles	0	14	88	1
	Sacramento	0	7	34	0
Colorado:	Denver	18	363	1542	29
District of Columbia:	Washington	23	493	2325	40
Florida:	Jacksonville	0	20	205	1
	Miami	0	3	8	0
	Tampa	5	47	563	8
Georgia:	Atlanta	24	308	2350	39
Idaho:	Boise	3	50	270	5
Illinois:	Chicago	32	1006	6351	74
	Peoria	38	1117	12773	113
	Springfield	39	780	8512	89
Indiana:	Indianapolis	37	2130	13073	124
Iowa:	Iowa City	34	735	8378	83
Kansas	Wichita	38	802	5441	73
Kentucky	Louisville	34	1246	7492	84
Louisiana	New Orleans	20	295	2157	34
Maine:	Bar Harbor	5	76	426	8
	Eastport	4	43	280	6
	Upper Dam (Rangeley Lakes)	1	69	139	2
Massachusetts:	Boston	10	140	790	15
	Nantucket	12	309	952	20
Michigan:	Alpena	13	192	1124	21
	Detroit	30	1232	4913	67
	Flint	26	1110	9136	83
	Frankfort	32	720	4801	63
	Isle Royal	1	48	133	2
	Marquette	13	286	993	21
	Petoskey	8	118	669	13
	St. Ignace	8	168	687	13
	Sault Ste. Marie	5	39	197	6
Minnesota:	Duluth	29	250	2476	44
	Minneapolis	33	1130	7096	80
	Moorhead	27	1021	4687	61
	Rochester	30	397	4620	67
	Tower	4	46	253	6
Mississippi:	Biloxi	4	40	446	7
	Vicksburg	23	159	1665	33
Missouri:	Kansas City	38	905	7579	85
	St. Louis	36	1625	8225	93
Montana	Miles City	2	58	219	4
Nebraska:	Lincoln	30	274	2939	63
	North Platte	12	98	691	16
	Omaha	36	1029	8114	87
Nevada:	Reno	0	4	12	0
New Hampshire:	Bethlehem	3	48	262	5
New Jersey:	Atlantic City	18	391	1692	30
New Mexico	Roswell	2	44	350	4
New York:	Buffalo	35	2000	8992	100
	Coney Island	15	120	1327	23
	Lake Placid	5	59	206	7
	New York City	20	254	1575	30
	Saranac Lake	3	46	350	5

TABLE I—CONT'D

PLACE		AVERAGE NUMBER OF HAY FEVER DAYS PER SEASON	MAXIMUM ATMOSPHERIC CONTAMINATION	AVERAGE SEASONAL TOTAL	RAGWEED POLLEN INDEX
North Carolina:	Asheville	31	630	4070	58
	Hatteras	41	650	4646	71
	Raleigh	18	337	1340	28
Ohio:	Cleveland	29	1270	5318	68
	Toledo	35	1134	9949	96
Oklahoma:	Oklahoma City	37	568	4715	66
Oregon:	Portland	0	0	0	0
Pennsylvania:	Philadelphia	24	398	2607	41
	Pittsburgh	28	1006	3873	57
Rhode Island:	Block Island	20	336	1490	31
South Carolina:	Charleston	7	107	571	11
South Dakota:	Mobridge	7	75	487	10
	Pierre	8	246	633	14
Tennessee:	Knoxville	26	562	3455	49
	Memphis	35	645	4323	63
Texas:	Amarillo	0	15	146	1
	Brownsville	20	375	1980	24
	Corpus Christi	15	381	2327	30
	Dallas	42	924	4731	75
	El Paso	0	9	110	1
	Galveston	14	666	3012	36
	Houston	28	1025	5961	68
	San Antonio	19	112	1300	27
Utah:	Salt Lake City	1	31	297	3
Virginia:	Richmond	19	151	1499	28
Washington:	Seattle	0	0	0	0
	Spokane	0	2	8	0
Wisconsin:	Eagle River	8	140	718	13
	Milwaukee	30	1485	6561	78
	Plum Island (Door Co.)	22	434	2679	40
Wyoming:	Lander	14	184	1333	23
Canada:	Cochrane, Ont.	1	38	114	2
	Father Point, Que.	0	21	96	1
	Montreal, Que.	10	132	744	15
	Ottawa, Ont.	7	81	542	11
	Parry Sound, Ont.	5	101	456	8
	Port Arthur, Ont.	4	134	312	7
	Prince Albert, Sask.	0	5	6	0
	Toronto, Ont.	14	231	1251	23
	Winnipeg, Manit.	4	252	374	8
Mexico:	Mexico City	0	9	34	0
	Tampico	2	56	279	4

effective refuge from ragweed pollen, for we know that pollen may be blown in toxic amounts for hundreds of miles.

A single premature attempt to apply the pollen counting methods of Blackley was made in 1888 by Professor Samuel Lockwood[3] of Freehold, New Jersey, who, because of his own hay fever, was accustomed to spend his summers at Bethlehem, New Hampshire. During the season of 1889 he exposed two series of daily pollen slides, one in his home town in New Jersey, and one at Bethlehem. The exact results of this study have not been preserved, but the report states that large

quantities of ragweed pollen were found on the slides at Freehold, and none at all at Bethlehem. Unfortunately, the study was not continued because the hotel keepers in the White Mountains refused to furnish funds for such research.

Sixteen years ago, Dr. Scheppegrell, the American apostle of pollen research, even though experienced in atmospheric pollen study, laid hold on no better method of compiling a list of hay fever resorts than that of sending a questionnaire to the Boards of Health of the various states. More than half of the states reported favorably on some part of their own area. This is the list which has for years been distributed by the United States Public Health Service.[4]

The purpose of the present briefly condensed report is to record the results of a second season of study of the ragweed pollen content of the air in the fringes of the ragweed belt, and to suggest a method of combining in a single index figure the several factors which constitute the ragweed pollen hazard in a given place. In the application of the pollen index the factor has been worked out not only for the points in the border areas but, for purposes of comparison, in all places in which uniform atmospheric studies have been carried on during the past eleven years—almost 100 localities. Most of the test stations used in 1934 were used again during the past season, and slide exposures were made in almost every instance by the same persons who had assisted the year before. Again, the slides were handled largely by regular and volunteer observers of the United States Weather Bureau. On account of the overwhelming evidence of the absence of ragweed and ragweed pollen in the extreme Pacific Northwest, no further studies were made in that region for 1935. For the same reason no investigations have yet been carried on in western Canada or Alaska. Likewise, the comparatively unimportant ragweed situation in the southwestern states and Mexico was not again studied. Three new stations were added, Plum Island, Wisconsin (near Washington Island at the tip of the Door County peninsula), Alpena, Michigan, on the west shore of Lake Huron, and Eastport, Maine.

In Table I and the map presented in Fig. 1, the appraisal of each place as a hay fever resort is based on three measurable factors: the number of days in the season when pollen concentration reaches 25 granules per cubic yard of air, the maximum daily concentration, and the total annual pollen count. Other important considerations affecting the convenience and comfort of the hay fever sufferer, such as accessibility, hotel accommodation, temperature, and other weather conditions, are not considered as being within the scope of this study, and are therefore not included in the pollen index which covers only the three statistical factors noted above. I have selected Buffalo as the 100 point on an arbitrary scale and have assigned one point in the score to each point in the first column of the table, one point to each

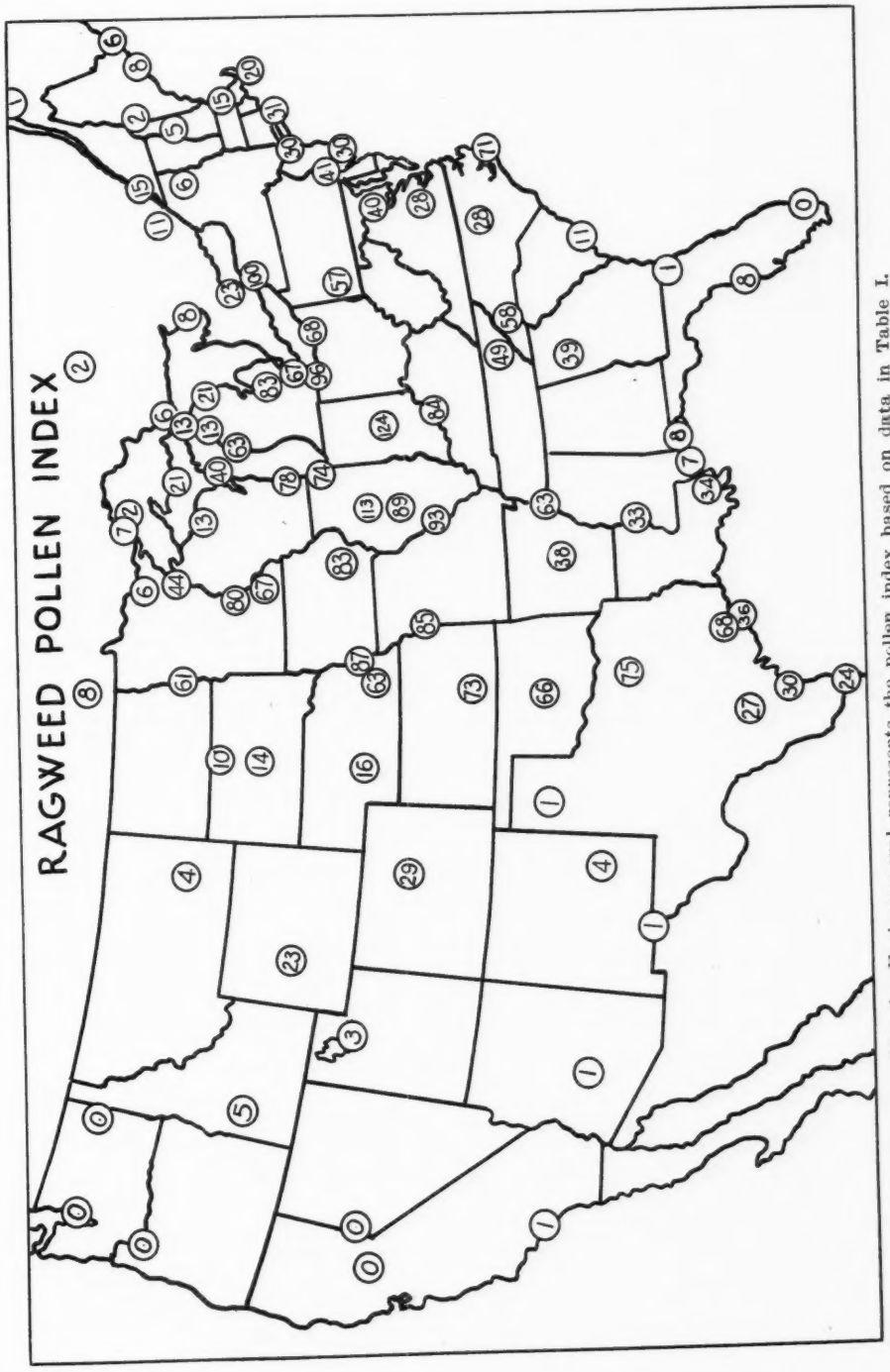

Fig. 1.—Each numeral represents the pollen index based on data in Table I.

100 points in the second column, and one point to each 200 points in the third column. The "number of days of hay fever per season" as noted in the first column of the table is the number of days on which the pollen slide showed 25 or more ragweed pollen granules per unit area (1.8 sq. cm.). The "maximum atmospheric contamination" is the number of ragweed pollen granules on the slide which showed the greatest contamination during the year or years when the studies have been carried on. The "seasonal total" is the sum of the pollen granules found on the unit area of all slides exposed during the ragweed season.

The accompanying map and table will be found useful to physicians in their study of the problems of the ragweed sensitive patient and to all who are interested in this menace to public health.

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Special Reports

REPORT OF THE INVESTIGATION AND SUCCESSFUL TREATMENT (PREVENTIVE) OF DERMATITIS RESULTING FROM THE HANDLING OF TULIP BULBS

A. H. W. Caulfeild, M.B., F.R.C.P. (C.), Toronto, Canada

M. C., who was referred to me in November, 1934, gave a history of a seasonal exposure for four years to tulip bulbs with a resulting dermatitis of great severity for the last three years. Although other plants and bulbs were handled at the same time, both he and two associates of his were convinced that the dermatitis was caused by the tulip bulbs. The two associates (of a total of five) similarly employed were but slightly affected. Bertwistle[1] gives a description of the extent and severity of this condition under the name tulip fingers as it affects those employed in the tulip bulb industry.

Patch tests showed in brief a severe and prolonged dermatitis to the ether soluble fraction obtained from minced tulip bulbs. No reaction was obtained with the tulip mass following ether extraction—nor to a glycerin and saline extraction.

Scratch tests were negative to all fractions. No evidence could be obtained to show skin sensitizing antibodies by the Prausnitz-Küstner reaction to either a scratch or a patch test applied to areas sensitized with undiluted serum.

Preventive treatment with the ether soluble fraction taken up in mazola oil prevented the dermatitis for the first time in five years. The injections were given intramuscularly and were without reaction or discomfort.

Patch tests following treatment showed a marked reaction to what were evidently stronger preparations than the one used for therapeutic purposes. These, however, differed from the tests before treatment in that the erythema subsided within forty-eight hours and the vesicle healed rapidly. A second patient (tested at this time) suffering to only a slight extent during the 1936 "bulb season" showed a mild erythema to only two of five different "therapeutic solutions" after a similar twenty-hour application. The dermatitis, however, in this case progressed to vesiculation and lasted for several weeks in a manner similar to the results obtained with the first case before treatment.

Read at the Annual Meeting of the Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 2, 1936.

The positive results obtained with patch tests and the negative results with scratch tests and the Prausnitz-Küstner reaction with these two cases correspond closely to the usual findings obtained with cases of ragweed dermatitis.

Coca[2] has suggested that contact dermatitis such as these two cases and the usual case of ragweed dermatitis should constitute one of three subdivisions of allergic dermatitis. A second subdivision includes cases in which the dermatitis is induced by inhalation or ingestion and in which one would expect to obtain positive scratch (or intradermal) tests and a positive Prausnitz-Küstner reaction.

In the following respects these two groups of cases are diametrically different.

1. The excitant in the contact group is found in the ether soluble fraction, i.e., nonantigenic; whereas with the atopic group it is in the watery soluble fraction, i.e., an antigenic fraction.

2. The modus operandi in the contact group is by actual contact; whereas with the atopic cases the lesion is induced not by contact but by inhalation or ingestion.

3. With the contact group heredity would appear to exert no influence; whereas with the atopic group this factor is seemingly as important as with cases of hay fever or asthma.

4. By means of differential skin tests the following results are obtained: (a) The patch test is positive with contact cases and negative with atopic cases. (b) The scratch or intradermal test is negative with contact cases and positive with atopic cases. (c) No evidence of skin sensitizing antibodies in the serum of the contact cases has been reported by the usual Prausnitz-Küstner reaction or by applying a patch test to the serum sensitized site. The Prausnitz-Küstner reaction is positive with cases of atopic dermatitis.

These differences are so pronounced that the question arises as to the helpfulness of including such cases of contact dermatitis under the general heading of allergic diseases. The terms allergic and atopic are usually interchangeable; with such a classification as that suggested by Coca the word atopic should be restricted and differently defined from the term allergic.

These cases of contact dermatitis unquestionably demonstrate a specific skin idiosyncrasia (or allergy) which can be prevented by the intramuscular injection of a fraction of the vegetation which has been labeled by the immunologists as nonantigenic in character.

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DISCUSSION

DR. FRANCIS M. RACKEMANN, Boston.—I should like to ask Dr. Caulfeild how much local reaction there was following the therapeutic doses given subcutaneously.

And I should like to ask how many controls he had that gave negative patches.

The classification is very important. The kind of eczema that he called allergic dermatitis is typical, and has a mechanism quite comparable to that of hay fever and asthma. Like the others, it depends upon a general sensitiveness with the cause of trouble reaching the skin through the blood stream underneath. It needs a name to designate it and to distinguish it from contact dermatitis. On the other hand, contact dermatitis is also allergic because it depends upon a special form of local tissue sensitiveness of the skin itself, with cause of trouble reaching the skin directly, from on top. I believe Dr. Sulzberger has some ideas on that.

DR. MARION B. SULZBERGER, New York.—I am afraid I have nothing new to add to the classification. I think we are all agreed that there are two very distinct types of dermatoses which represent the usual eczematous and eczema-like allergic skin manifestations. One of these is the contact type dermatitis which Dr. Caulfeild has described. This is certainly allergic; for the proof that it is based upon specific acquired alterations in the capacity to react, that is, upon allergic sensitization, is undeniable. Experiments with primrose, with paraphenylendiamine, with ivy oil, with mercury, with orthoform, with mesothan, and with innumerable other contact excitants, have proved the allergic nature of this type of dermatosis far beyond the point in which allergy has been proved as the underlying mechanism in hay fever or asthma or atopic dermatitis. So that contact type dermatitis must be considered the most firmly established, classic and undeniable form of skin allergy. I believe it is important to be able to distinguish very sharply, as Dr. Caulfeild has done, between atopic dermatitis and contact dermatitis. The allergens in these two forms are different: in the first form they are the usually so-called protein allergens; and in the second form they are usually simpler, smaller molecular substances, such as plant oils or other small molecular substances as metallic salts, anesthetics, dyes, formalin, other drugs, and so forth. Moreover, the tests which must be employed are entirely different: in the atopic group, scratch or intracutaneous tests; in the contact group, patch tests. As Dr. Caulfeild brought out, one can scratch these contact dermatitis patients until the cows come home with the various fractions of allergens and one will get no reactions. One has to use the patch test. Furthermore, it is undeniably important, but nevertheless remarkable, that it is in this type of skin allergy that it is precisely in contact dermatitis due to plant oils, that desensitization or hyposensitization is of great practical value; whereas in the atopic dermatitis, all my attempts at desensitization with protein allergens have met with very little, if any, success.

As I have said, it is indeed remarkable that in ragweed dermatitis, in ivy dermatitis, in tulip bulb dermatitis, and in a whole series of these plant oil dermatitides of the contact type, specific treatment and specific prevention by means of the injection of oil or fat soluble fractions give such good results.

That is important because all these plant oil cases are only modest representatives of a vast number of allergic dermatoses of similar or identical pathogenesis. For instance, most occupational dermatitides belong to this group. In all these innumerable dermatoses of the contact type due to substances other than plant oils, we have as yet had no success in specific prophylaxis and treatment. It is therefore most urgent that we find out why it is that the method works so regularly in the case of plant oils; and why it has as yet been unsuccessful in the hyposensitization treatment or prophylaxis of the contact dermatitides as a whole.

I believe that this is perhaps the one outstanding problem facing modern dermatology, and for this reason time is well spent in an exact study of the hyposensitization mechanism in the plant oil cases. Perhaps when we know more regarding such questions as the exact quantitative conditions, the most propitious route for the administration of allergens and the most advantageous vehicles, we may achieve a hyposensitization method useful in treatment and prophylaxis of all contact type eczematous sensitizations. I would here include even the superficial, eczematiform and dyshidrotic, fungous skin diseases, which are in my opinion essentially sensitizations of eczematous type.

DR. CAULFEILD.—Regarding the local or general reactions, there were none. I should add that the initial dose was diluted to one in 20,000 in mazola oil. I had, in the beginning, no idea regarding what doses could be used with safety. With increasing confidence I quadrupled it, and so forth, and brought it up to 0.4 c.c. of what I called my saturated or stock solution. The amount of material obtained from the ether extract was too small to measure accurately or to weigh for the first therapeutic set which was the one actually employed.

With reference to controls, these consisted of mazola oil itself, ragweed, and other pollen oils. At the time I happened to have a case of ragweed dermatitis and used ragweed extract as the chief control in these two cases. In a like manner I used the tulip extract as one of the controls with the case of ragweed dermatitis. All controls were negative.

As the discussion on classification was stopped by the time limit, I have little to add beyond stressing the fundamental differences outlined in the chart which I used to illustrate these.

CONTACT DERMATITIS*

Cases Caused by Oil of Cloves and by Oil of Camomile Tea (Anthemis Cotula)

Louis Sternberg, M.D.
New York, N. Y.

DURING the past five years many cases of contact dermatitis have been reported induced by various agents. The list of the excitants is very large but does not include oil of cloves, nor the oil of camomile.

Rowe[1] described a patient sensitive to camomile with which he secured positive patch tests. Apparently the patient was tested with camomile leaves but not with the oil. Weber[2] in a long list of skin irritants included camomile tea but not the oil.

The cases presented here are interesting because both these ingredients are used extensively: oil of cloves in various cosmetics, drugs, candies, tooth powder, and shaving soaps; camomile tea as a hair dye, and also by many foreigners as a lotion after bathing.

CASE REPORTS

Case 1.—M. O., salesman, twenty-eight years old, has been under our care for early hay fever for the past four years. On February 12, 1936, he inquired about an itch over his face. He never had suffered from any skin disease prior to the present attack of about four months' duration. This began with slight itching and reached a stage where he now finds difficulty in shaving on account of the added irritation. He formerly used a shaving powder, but for the past six or seven months he had used Ingram's shaving cream.

Physical examination showed that the inflammatory lesion covered all the bearded region of his face, and consisted of a marked dermatitis. He was advised to go back to the former soap, and the skin lesion cleared up within two weeks.

The manufacturers of the above named cream were very cooperative in sending me the ingredients of their soap. The patient was patch tested with all, and gave a positive reaction to the oil of cloves. A patch test with the same brand of soap, not perfumed, gave a negative reaction. The tube containing all ingredients gave a positive patch test.

Case 2.—L. G., a woman, fifty-four years old, had suffered from asthma for many years, and for the past six or seven months complained of an itch and rash over the scalp and neck.

Her blond hair made us inquire what were the ingredients of her hair preparation. We were informed that these consisted solely of peroxide of hydrogen followed by a wash of an infusion of camomile leaves applied twice weekly for the past few years.

Her skin had begun to itch about one year before she sought relief, but reached the present stage during the past four or five months.

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*From the Allergy Department of the Beth Israel Hospital.

On physical examination she presented a marked dermatitis over the scalp, neck and upper part of the chest and back.

A patch test with the infusion of camomile tea gave a negative reaction. A patch test made from the oil of this material gave a positive reaction, with blistering of the patch area. Peroxide patch was negative. The withdrawal of the infusion from the scalp completely cleared the skin in six weeks.

SUMMARY

Two cases of contact dermatitis are presented, one caused by the oil of cloves, the other by the oil of camomile tea. The lesions in both these patients disappeared promptly upon the removal of the above mentioned contactants.

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17 PARK AVENUE

DERMATITIS CAUSED BY CREOSOTE BUSH

LESLIE M. SMITH, M.D.
EL PASO, TEXAS

THE list of plants which are known to be capable of sensitizing the human skin has grown considerably during the last few years, due to the wider application of the patch test in the diagnosis of dermatitis. It seems desirable to report all new contactants.

In view of the abundant growth of the creosote bush over a large part of the arid section of the southwestern United States, the possibility of

Fig. 1.—Creosote bush growing in the desert.

skin sensitization to this plant, and resulting dermatitis, should be kept in mind by physicians of this section. I know of no other reported cases of dermatitis from this shrub. Creosote bush, *Covillea glutinosa,* is an evergreen which grows extensively over the desert regions of western Texas, New Mexico, and Arizona. (Fig. 1.) One can hardly walk or ride in the desert without brushing against it frequently.

CASE REPORT

Mr. J. A. S., an American, on December 9, 1935, presented an erythematous and vesicular dermatitis of the face, upper part of the neck, and backs of the hands, which began the night previously. The patient had had several attacks of dermato-

phytosis in the past, ivy poisoning, and urticaria several times from various foods. There was no family history of allergic phenomena. A few hours before the acute dermatitis began, he had gathered a desert shrub, which he thought was sage, for Christmas decorations. During the next few hours the face and hands began to itch, and dermatitis and moderate swelling developed. On examination the shrub proved to be the creosote bush. Patch tests with the leaves were made on the forearm and on the lower part of the neck below the eruption. When examined forty-eight hours later, both test areas had reacted strongly with erythema and vesiculation. Similar tests on persons with normal skin did not cause reaction. Wet dressings of diluted Burow's solution were applied continuously, and further contact with the offending plant was avoided. The dermatitis rapidly disappeared during the next few days and has not returned.

929 First National Bank Bldg.

CASE OF RESPIRATORY ALLERGY DUE TO INHALATION OF GRAIN SMUTS

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Minneapolis, Minn.

As Feinberg has shown, allergic reactions to fungi are not rare or unusual. He pointed out that Van Leeuwen in 1924, in discussing the relation of bronchial asthma to climate, insisted that asthma may be caused by the air-borne spores of molds, and suggested that "sensitization and skin reactivity to certain allergens, such as feathers, hairs in grain, and the molds which infest these substances, were actually responsible for these."

Cadham the same year reported cases due to grain rusts. A few years later other observers reported cases due to the more common air molds and yeasts. Stakman and his coworkers made observations as early as 1923 on spores of the upper air.

Feinberg called attention to the wide perennial prevalence of molds about Chicago and made routine mold and pollen counts, pointing out that most mold spores are smaller than pollens and are of higher protein content, and more prevalent during the pollen season than the pollens themselves, and "may reasonably be expected to contain potent allergens." His routine tests with fungous extracts and yeasts on allergic patients, mostly of the respiratory type, were illuminating.

Of 243 patients with respiratory allergy, 28 per cent gave positive cutaneous tests to one or more of the fungous extracts enumerated; and of 590 patients, mostly of the respiratory allergy type, 11 per cent reacted to the yeasts. The majority of these patients were sensitive to the ragweed pollens, and this explains the puzzling features of many of these cases which show there were other factors than pollen sensitization. Since this article was written, Brown reporting his results with routine mold sensitization tests casually mentioned smut fungi as one of the allergens used. We can find no definite case reports, however, of smuts being the prime factor in producing asthma or where they were found present in fairly large numbers in the sputum of an asthmatic individual who gave a definite history of having asthma when exposed to them and showing a predominating marked sensitivity to their extracts.

It is well known that a careful routine study of sputum smears of asthmatic persons will reveal molds in patients who are not sensitive to them. It has not, however, been the experience of one of us who has made extensive studies of the bacteria in the sputums of asthmatic persons to find mold spores frequent or numerous in these smears.

Observations we are now making would indicate that in milling districts smuts may play equally as important a rôle in respiratory allergy as do the commoner molds, and frequently augment the severity of the grain sensitive patients. Because of periods of drought, low humidity, and high winds in the Northwest during the past few years, the spore content of the air has frequently been extremely high. During the rust epidemic of 1935 as many as 980,000 per square foot were deposited a few feet above the ground during a twenty-four-hour period, and the number not infrequently reached 1,000,000.

CASE REPORT

L. M. S., aged forty-eight years, was first seen October 28, 1935. He complained of having had asthma for twenty-two years, that he did not have a trace of it before that time, that the onset was sudden and very severe, and that he noticed it

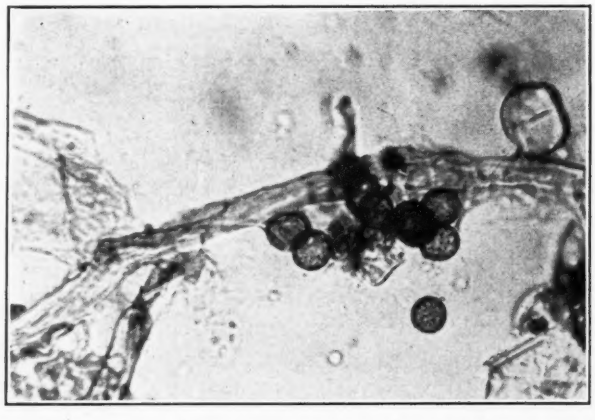

Fig. 1.—Photomicrograph of sputum showing clumps of spores of corn smut, *Ustilago zeae*. (These spores were compared with spores from a corn smut gall and agreed perfectly in size, shape, echinulation, and other essential characters. The echinulations do not show well in the photograph but were clearly visible under the microscope.) Magnified about 500 diameters.

first when working about grain elevators or flour mills. He would get it any time during the year if his duties took him near grain elevators or flour mills or wherever there was flour dust. He stated that he had some asthma during the hay fever season but not as severe as when he was exposed to flour dust. He had not entirely eliminated bread from the diet. As a rule, he obtained relief from ephedrine and amytal or epinephrine. He had moderate hay fever also during the fall season.

During the fall of 1935 he suffered from recurrent colds. He worked for a local power company which had various substations about the city and suburbs, and his duties required him to be located and working about in one of them in the center of the milling district of Minneapolis. Invariably about eight hours after he started working in this particular substation he would develop severe paroxysms of asthma and become helpless. There was nothing unusual about his physical examination. Skin tests were done with pollens, grains, foods, animal emanations, and yeasts. He was found mildly sensitive to ragweed and yeasts but not to the grains. Also, tests were made with extracts of some common air molds and other fungi to determine their factor in this particular case: three species

of Penicillium, Chaetomium sp., *Aspergillus fumigatus, A. glaucus, A. nidulans, A. niger* were negative, and Alternaria was mildly (one-plus) positive.

While we were preparing to give him some iodized oil, he coughed up material that contained black flakes which microscopically contained spores resembling smuts, and it occurred to one of us that he was allergic to one or more of the smut spores. The patient was instructed to place plates about the station and collect the dust. Sodium hydrate extracts of this dust produced a very definite skin sensitiveness.

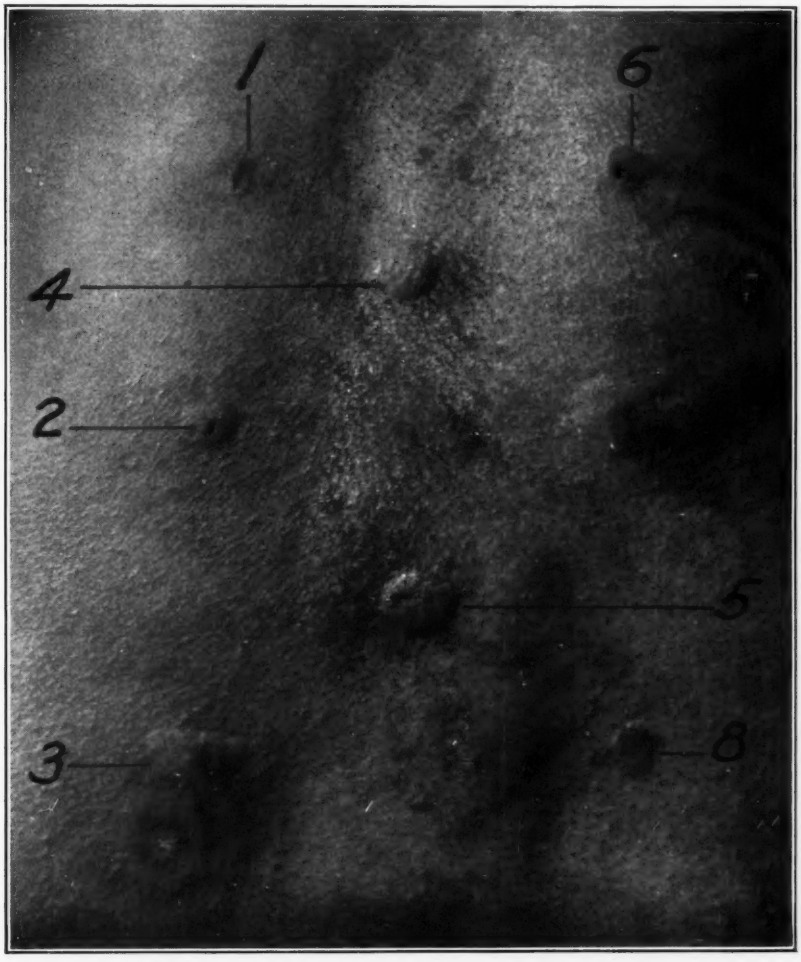

Fig. 2.—(All scratch tests except 4 and 5.) 1, Control; 2, wheat smut, *Tilletia levis;* 3, corn smut, *Ustilago zeae;* 4 (intradermal) 1:1000 sorghum smut, *Sphacelotheca cruenta;* 5 (intradermal) 1:1000 combined smut extracts; 6, rye smut, *Urocystitis occulta;* 7, wheat smut, *Tilletia tritici;* 8, stem rust of wheat, *Puccinia graminis tritici.*

The sputum smears were studied, and the following smut spores were found: (1) *Ustilago zeae,* corn smut; (2) Ustilago sp. with smooth spores, scattered in clumps; (3) *Tilletia levis,* one of the organisms causing stinking smut of wheat.

The smut spores, however, were relatively scarce in proportion to the number of spores of other fungi. There apparently were quite a number of yeasts, spores of Penicillium, and a number of other spores that could not be identified.

Fourteen of the commoner smuts of wheat, barley, oats, rye, sorghum, millet, and corn, and urediospores of *Puccinia graminis tritici* were then tested. Scratch tests and puncture tests with a Taylor knife using solid extracts made with $\frac{N}{10}$ NaOH solution showed the results given in Table I.

TABLE I

RESULTS OF SCRATCH AND PUNCTURE TESTS WITH VARIOUS SMUTS AND WITH STEM RUST OF WHEAT

Wheat—stinking smut—*Tilletia tritici*	3 plus
Tilletia levis	2 plus
loose smut—*Ustilago tritici*	1 plus
Barley—covered smut—*Ustilago hordei*	1 plus
intermediate smut—*Ustilago medians*	plus minus
loose smut—*Ustilago nuda*	1 plus
Oats—covered smut—*Ustilago avenae*	1 plus
loose smut—*Ustilago levis*	negative
Rye smut—*Urocystis occulta*	1 plus
Sorghum—covered kernel smut—*Sphacelotheca sorghi*	2 plus
loose kernel smut—*Sphacelotheca cruenta*	1 plus
head smut—*Sorosporium reilianum*	negative
Millet—smut of foxtail millet—*Ustilago crameri*	1 plus
Corn smut—*Ustilago zeae*	2 plus
Puccinia graminis tritici (rust)	1 plus

Extracts of these smuts and rusts were made and furnished for purposes of desensitization by the Arlington Chemical Co., and the patient is being desensitized with very satisfactory results.

Fig. 1 is a photomicrograph made from the patient's sputum smears, and more detailed culture studies are now being made. Fig. 2 is a photograph of the results of the skin tests made with the smut and rust extracts.

It will be noted that the two species of stinking smut of wheat, corn smut, and the covered kernel smut of sorghum caused the most pronounced reactions. Spores of the stinking smuts of wheat may be numerous in mill dust, as a single smutted kernel of wheat may contain from 6,000,000 to 9,000,000 spores, according to Heald, and Buller computed the number in a single large kernel (smut ball) at 12,125,000. At harvesting or threshing time the spores may be very numerous in the air. Heald estimated that more than 5,000,000 may fall on each square foot of soil in the wheat growing districts of the Palouse country of eastern Washington. Countless billions of spores of the corn smut fungus may be produced in a single cornfield of the Middle West and are widely disseminated by the wind, as is clear from studies of spores in the air.

SUMMARY

There is indication from this preliminary observation that grain smuts may be solely responsible for respiratory allergy, particularly asthma. The case reported shows no skin sensitiveness to the grains but definitely to various grain smuts which were demonstrated in the sputum smears. These produced clinical asthma only on exposure to the dust containing them in large amounts. The patient is responding to treatment by desensitization.

We are very grateful to Dr. J. H. Frazer of the Biological Department of the Arlington Chemical Co. for furnishing us with the extracts of smuts and rust for desensitization purposes, as well as the common air molds for skin testing.

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ANOTHER PLANT CAUSING HAY FEVER IN CALIFORNIA*

Coprosma Baueri Endl. Mirror Plant

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THE list of plants causing hay fever in California is already so extensive that we hesitate to make additions. However, an ornamental shrub, *Coprosma baueri*, Fig. 1, has come to our attention because of its having the typical characteristics of hay fever producing plants: inconspicuous flowers and light, wind-blown pollen. Further-

Fig. 1.—*Coprosma baueri* Endl. Left, female flowers; right, male flowers.

more, of great importance is the fact that it is planted in great numbers in gardens, parks, and along streets throughout the state as hedges, bank and ground covers, and for mass planting. Tests made with an extract of the pollen showed positive reactions.

Coprosma baueri may be easily recognized by its leaves, whose upper surfaces are dark green, smooth, and glossy and whose lower surfaces are pale green and have sunken pits at the bases of the veins. The leaves are arranged in opposite pairs on the stems. The small, inconspicuous, greenish white flowers are dioecious (male and female

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flowers on different plants), so only half of the plants are capable of producing pollen. The pollinating period is from early April to late June.

The pollen grains, Fig. 2, are irregularly spherical or often triangular in shape, with sunken depressions and pits. They have a mean average diameter of 35 microns. When moist they show, in median

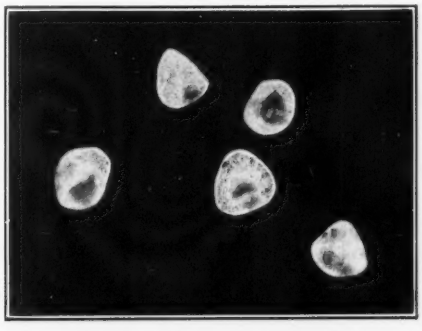

Fig 2.—Pollen grains ×250.

optical view, one to three germinal pores and a clearly defined exine. The iodine test shows the presence of protein but no starch.

The tests with *Coprosma baueri* pollen extract have been carried on at the University of California Hospital under the direction of Dr. Wm. C. Deamer. Of 58 patients, 13 gave positive skin reactions to *Coprosma*. These results are such that it seems advisable to recommend that this pollen be included in the routine testing of hay fever patients in California.

Annual Review

ALLERGY AS RELATED TO OTOLARYNGOLOGY AND OPHTHALMOLOGY

Literature for 1936

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IN THE following review of the literature on the subject of allergy from the standpoint of ophthalmology and otolaryngology for the year 1936, only those publications which have presented new and important observations will be considered.

Contributions on the fundamental aspects of allergy of the nose and paranasal sinuses have been confined chiefly to biochemical investigations of nasal secretions and nasal tissues. From the standpoint of diagnosis, several observers have emphasized the importance of cytologic examinations of the nasal secretions. That the otolaryngologist is becoming more allergy minded is exemplified by the increasing number of observers who call attention to the importance of considering allergy in the diagnosis of sinus disease. Further studies on the results obtained in asthma by surgical treatment of the sinuses confirm those reported by other recent observers. Several papers on the ionization treatment of the nasal mucosa for perennial nasal allergy and hay fever indicate some difference of opinion still existing as to the value of this method. Increasing interest in allergy in its relation to ophthalmology is manifest in a number of interesting articles on this phase of the subject.

BIOCHEMISTRY

A biochemical study of nasal mucin was undertaken by Buhrmester.[1] She found that nasal mucin is not identical with any mucin from other tissues or secretions. The polysaccharide of mucin was obtained free from protein and identified only by its general physical characteristics. It was shown that the viscosity of mucin is decreased by increase in temperature and by the presence of ionizable salts. The stirring of mucus decreases the viscosity.

According to the investigations of Buhrmester and Wenner,[2] nasal polyps and normal mucous membrane contain a histamine-like substance in approximately equal amounts in the moist tissue. Calculated on the basis of dry weight of the tissue, polypoid tissue contains more

histamine than does normal membrane. It was found that the nasal secretion from persons with allergic rhinitis does not have depressor activity when injected intravenously. The hydrolyzed secretion contains much less histamine-like substance than do polyps, calculated on actual protein values. Histaminase was not found to be present in allergic nasal secretions. It is suggested that the increase in mineral content of the nasal discharge with the resulting effect on permeability, difference in potential and acid-base equilibrium, are factors to be considered in studying the formation of polyps and other allergic manifestations.

Deilmann and Kutscher[3] found in studies on the behavior of the protein nitrogen in the secretions in acute and chronic disorders of the accessory sinuses, that a single determination of the protein does not permit a conclusion as to whether the process is acute or chronic. Serial examinations reveal, in cases of acute sinusitis, great, irregular fluctuations of the protein content between 1 and 9 per cent. In cases of chronic sinusitis the protein content is more stationary, with variations from 3 to 5 per cent.

A few further observations on the reaction of the nasal mucus were reported by Tweedie.[4] Previous findings, in general, were confirmed. It was found that the normal nose possesses a mucus with a reaction varying from pH 6.5 to pH 7.4, and a nonculturable content. In acute rhinitis it was found that the normal reaction is not affected for two or three days, and during that time no culturable content is present. After that time a culturable growth of the common inflammatory organisms is obtainable for some three weeks. It was stated that chronic rhinitis may exist in connection with purely mechanical factors, for example, obstructive deviation of the septum, postoperative conditions in clean cases or only as the result of traumatic lesions; also in hay fever, so-called spasmodic rhinorrhea and asthma, and even in some cases of rhinitis associated with sinusitis and polyps or syphilis. In all these cases an unaltered reaction of the nasal mucus and a nonculturable content may be found. On the other hand, Tweedie states that a chronic rhinitis may show abnormal alkalinity and reveal a culturable content obtained on a medium corresponding to the reaction of the mucus or demonstrable only on a medium of greater alkalinity.

As far as cultures were concerned, no growth was obtained from any nose on a medium at pH 6.5 with the exception of *Staphylococcus aureus* and *Staphylococcus albus*, which grow freely on any medium. *Staphylococcus albus* was regarded merely as a result of contamination and not as pathogenic. The usual findings are some forms of streptococcus. It was further stated that this bacterial growth in the nose, therefore, does not take place until and if the normal reaction of the nasal mucus becomes alkaline, and the growth must thus be regarded

as a secondary infection, virulent only when some other condition induces an alkaline reaction of the nasal mucus. It was also pointed out that a normal reaction of the mucus is not the only safeguard, since other factors must certainly take part; for example, lysozyme, the action of the cilia, and probably the presence of a structurally normal nose.

In 387 asthmatic patients examined by Griebel,[5] it was found that 293 presented evidence of the allergic form of the disease. The pathologic conditions in the nose varied from the presence of simple serous fluid to marked polyposis. Chronic suppuration was found in 176 of 293 patients. This incidence of chronic suppuration is much higher than that noted by other observers. Physicochemical examinations made of nasal polyps revealed a relatively high mineral content and a hydrogen ion concentration of from 7.52 to 8.3. It was concluded that albumin plays a decisive part as the hydrophilic colloid in the development of polyps.

In discussing the biochemical aspects of sinus disease, Ruskin[6] states that in the paranasal sinuses there is a mechanism favoring the transudation of discharge rich in nucleoproteins while in the nasal mucous membrane the secretory structure produces a discharge rich in mucoproteins. He further states that a loss in nucleoproteins from the sinus mucosa results in a hyponucleinemia, causing changes in the blood comparable to those occurring in nephrosis. The severe loss of secretions from the nasal and the pharyngeal mucosa is viewed as associated with the loss of mucoproteins, and these substances are used by the liver and kidney in the detoxicating mechanism and their deficiency is associated with the picture of acute toxic nephritis. Ruskin reports a series of 13 cases of nasal allergy, 5 of which are described in detail, showing marked benefit from the ingestion of nucleic acid (yeast). These observations, he believes, indicate that allergy is related to a depression of nucleic acid possibly secondary to chronic infection that has caused a continuous drainage of nasal secretion. He also found that the administration of nucleic acid was of benefit in cases of nasal polyposis. He concluded that the loss of nucleoprotein manifests itself as a deficiency in some cases and appears to be a disturbance of water metabolism related to nephrosis.

DIAGNOSIS AND TREATMENT

The value of the determination of the cytology of the nasal secretions in allergic and nonallergic individuals with nasal symptoms is exemplified in the extensive observations of Cowie and Jimenez.[7] The cytology of the nasal secretions was studied in allergic individuals free from infectious colds. Such types as pure hay fever, hay fever plus other sensitivities, multiple sensitization but not to pollen, and sen-

sitization with an associated epidermal sensitivity, were considered in one group. The second group of cases consisted of sensitized persons in whom the cytology of the nasal smears was studied during the period of infectious colds. Comparative simultaneous differential counts of the blood and nasal secretions were also made. On the basis of these studies the authors state that an eosinophile count in a nasal smear of from 20 to 25 per cent indicates that the patient is allergic. The percentage of eosinophiles seems to be greater in patients with epidermal sensitization. During an infectious cold, it was found that the neutrophiles predominate in the cytologic picture with or without varying percentages of eosinophiles. Comparative simultaneous differential counts of the blood and nasal smears did not show a definite relationship to each other. Attention was called to the fact that the typical pale, boggy, mucous membrane may not be present in nasal allergy but eosinophiles may be demonstrated in the nasal secretions.

Attention should be called to the fact that the computation of the number of eosinophiles and neutrophiles in nasal smears in terms of percentages is subject to considerable discrepancy unless the cellular distribution is uniformly even. For example, the clumping of eosinophiles in masses in the presence of a large number of neutrophiles is not infrequently noted in cases of nasal allergy with acute infection. Although the cytologic picture may be diagnostic of allergy, the relative proportions of the two types of cells in terms of percentages may not be significant. Considerable variation in the relative numbers of eosinophiles and neutrophiles occurs, dependent upon the particular stage of an acute rhinitis superimposed upon an allergic process. During the early stage of a cold, the neutrophiles may completely predominate the picture. As a rule, the number of eosinophiles shows a significant increase in the late stage of the cold when the neutrophiles begin to disappear.

According to the investigations of Hume,[8] the cytology of the nasal secretions is of indispensable value in the diagnosis of all types of rhinosinusitis. He emphasizes the importance of the demonstration of eosinophiles in the nasal secretions in the diagnosis of allergy. He also discusses the significance of neutrophiles, lymphocytes, monocytes, and their relation to the various types of sinusitis.

Kállos[9] made a study of 125 cases of nasal and tonsillar diseases in which the secretions were examined for eosinophiles. In the nasal cases, consisting of vasomotor rhinitis and nasal polyps, eosinophiles were found to be present in from 10 to 50 per cent. An eosinophilia was also demonstrated in secretions expressed from the tonsils in rheumatic patients. Definite eosinophilia was also demonstrated in the tonsils upon histologic examination. Similar studies in nonrheumatic

patients revealed no eosinophilia. Kállos suggests a possible association between the tonsils and rheumatism on the basis of the local eosinophilia.

That the rhinologist has become allergy conscious in the diagnosis of sinus diseases is exemplified in many recent discussions of this subject. For example, Watkins[10] emphasizes that allergic phenomena are very common in nasal diseases and are likely to be overlooked unless careful history and examination are instituted. He further states that the failure to recognize the presence of allergy is responsible for lack of success in many operations on the nose. The relation of nasal polyps to allergy and the association of infection with nasal allergy were also discussed. The importance of the primary consideration of the allergic process before instituting operating procedures is advised.

In a general discussion of the subject of nasal allergy, Jay[11] calls attention to the diagnostic difficulties sometimes encountered in the recognition of these cases. The typical picture of a pale, boggy mucosa is not infrequently absent; therefore a great deal of dependence must be placed upon an accurate clinical history. The nasal manifestations of allergy should always be considered when dealing with patients with frequent colds, catarrh, and nasal obstruction. Jay emphasizes the importance of making a distinction among the following types of cases: (1) polyposis due to allergy, (2) polyposis due to infection, and (3) polyposis associated with allergy and infection. He adopts a conservative attitude toward surgery and points out that patients selected for operative interference should be carefully selected. He places primary importance upon the recognition and treatment of the allergic process.

In an analysis of a group of sinus cases from the standpoint of pathology, diagnosis, and treatment, the chief types to be considered are the allergic, the purely infectious, and the combined allergic and infectious. A great many analyses of sinus cases still appear in the literature without any consideration of allergy whatsoever. For example, Syme[12] analyzes a group of 100 consecutive cases of antrum disease which were operated upon by the radical Caldwell-Luc method. The chief symptoms in these cases were nasal obstruction, headache, postnasal discharge, sore throat, and anterior nasal discharge. Chronic cough and asthma were considered among the associated conditions. No histopathologic, bacteriologic, or cytologic studies were made in these cases. The pathologic conditions found in the antrum were as follows: mucous membrane edematous, 19; mucous membrane thickened, 13; pus present, 25; polyps present, 52; alveolar abscess, 2; atrophic membrane, 1; and suspicious malignancy, 1. It is clearly

evident that there is a very high incidence of allergy in this group of cases as indicated by the large number in which edema and polyps were found.

The incidence of sinusitis and nasal polyps in bronchial asthma was studied by Kelley.[13] His report was based on an investigation of 100 cases of bronchial asthma. According to x-ray examination, 89 per cent of the 100 patients showed a chronic hyperplastic sinusitis involving one or more of the sinuses. The remainder, or 11 per cent, showed no evidence of change. Sixty of the 89 patients with chronic hyperplastic sinusitis presented allergic nasal membranes; 23 of these patients were found to have nasal polyps. Kelley found that antral lavage revealed that in those cases with definite allergic reactions of the nasal membranes, the mucus content of the washings was relatively increased over that which was observed in cases with so-called simple hyperplastic membranes.

The relationship of sinusitis allergy and the common cold was discussed by Sewall[14] who calls attention to a number of important points in bacteriology and pathology. Acute infectious rhinosinusitis, chronic infectious rhinosinusitis, and chronic hyperplastic rhinosinusitis were all considered from these viewpoints. The importance of distinguishing the nasal manifestations of allergy from these various types and the recognition of combined forms of allergy and infection were emphasized.

In discussing the matter of allergy in relation to colds and coughs, Clein[15] brings out the point that children presenting the symptoms of frequent colds and chronic coughs are frequently subjected to various forms of treatment without results, such as removing the tonsils and adenoids, cold vaccine, vitamin D products, light treatments, sinus treatments, and climatic changes. It is emphasized that in the diagnosis of acute and chronic rhinitis, croup, paranasal sinusitis, laryngitis, tracheitis, bronchitis, the possibility of allergy must be considered. In children, acute and chronic infections may obscure a primary underlying allergic condition.

Clarke[16] emphasizes the importance of early diagnosis of allergic disease in the respiratory tract. He points out that in children before dyspnea begins there are usually prolonged premonitory symptoms, such as sneezing, blocked nose, mouth-breathing, cough or coryza. The acute attack of dyspnea is often the first incident that calls the attention of the family and the physician to the allergic nature of the ailment. The plea is made for treatment of early preasthmatic symptoms, emphasizing the fact that the majority of these children do not develop asthma if the early minor symptoms are treated. Attention was called to the rather frequent history of the onset of asthma after tonsillectomy. In these children with nasal symptoms diagnosis can

be easily established by the finding of an eosinophilia of the nasal secretions. In the event that a child suspected of having nasal allergy should have an acute rhinitis, the nasal secretions may show only neutrophiles. In these instances repeated examinations of the secretions should be made, especially after the acute infection has subsided.

Persky[17] investigated the causes of rhinorrhea in children, especially in those who had already had the tonsils and adenoids removed. Especial reference was, therefore, made to those children who gave a history of frequent colds and nasal discharge and who continued to have these symptoms after the tonsils had been removed. It was noted that certain systemic conditions may have a direct influence in these children. Reference was made to syphilis and other hereditary stigmas. In the malnutritional or marasmic group of cases, it was noted that frequent colds continued because of a lack of proper attention to this factor. Tuberculosis, diabetes, rickets and other conditions were also considered in this group. Treatment to combat the nutritional factor was advocated. Another group of cases was considered as of the lymphatic or endocrine type; often complicated by such conditions as otitis media, asthmatic bronchitis, rheumatism and nephritis. Finally, attention was called to the importance of proper diagnosis and treatment of the allergic type of nasal disturbances. The importance of the recognition of complicating infection was also stressed. Various types of local treatment were also recommended. In all children with rhinorrhea, regardless of whether they fall into any of the above-mentioned groups, the possibility of the nasal manifestations of allergy should always be carefully considered.

Bernheimer[18] made a study of the clinical results obtained by ionization of the nasal mucosa in a group of 25 individuals with hyperesthetic rhinitis and 10 with seasonal hay fever as compared with a similar group treated by the use of escharotics. The observations extended over a period of fifteen months. It is noteworthy that two patients suffering from hyperesthetic rhinitis developed anosmia following ionization treatment which persisted for four and seven months, respectively. In another instance a neuritis of the nasal ganglion with the typical pain syndrome described by Sluder persisted for three and one-half months. No complications were noted following the use of escharotics.

From these studies it was concluded that the histologic effects of ionization do not differ from those resulting from the application of escharotics. In neither was there marked evidence of fibrosis. It was found that the clinical course of hyperesthetic rhinitis was influenced in only 5 per cent of the 25 patients who were treated with ionization. Slightly better results were obtained with escharotics. The clinical course of hay fever was not altered by the use of either method.

Finally, it was stated that ionization of the nasal mucous membrane may be followed by complications which do not occur with the use of escharotics.

In a further report on the use of ionization in the treatment of hay fever and hyperesthetic rhinitis, Bryant[19] gives a tabulation of a small group of cases which were carefully followed. On the basis of the results obtained during the past year, as well as the further observation of patients treated a year ago and in spite of the fact that at the time of his first report he expressed a note of caution about becoming too enthusiastic too early in the use of the new method of treatment, he feels highly enthusiastic about the Warwick ionization treatment for hay fever and kindred conditions. He feels that it is deserving of wider interest on the part of general practitioners who are seeking relief for their patients from these conditions and wider knowledge and use on the part of properly trained otolaryngologists in whose hands this procedure safely and wisely belongs.

Hollender[20] reviews 150 cases and states that the result is a prolonged symptomatic palliation gratifying to both patient and rhinologist. The results in seasonal hay fever were disappointing, but he states that further research will be required before we can accept as final the reports which thus far have been placed on record. He concludes that zinc ionization is a simple and safe procedure in suitable cases of perennial vasomotor rhinitis and in asthma associated with vasomotor rhinitis and should be given a fair trial when conservative measures have failed.

Barrett[21] states that this form of treatment is good in some cases, of much value in others, and without benefit in the rest, but he feels that it will take considerably more investigation over several years before its true worth will be known.

The use of ionization in the treatment of hay fever and hyperesthetic rhinitis was also reported by Hurd.[22] Hurd uses the technic of flooding the nose with the electrolyte instead of introducing it on cotton strips. He reports that over 70 per cent of the patients with hyperesthetic rhinitis became symptom-free after treatment and that in the hay fever cases symptoms disappeared immediately after ionization in almost all instances.

According to the experiences of Shields,[23] nasal ionization with zinc sulphate is a valuable method of treating hay fever and vasomotor rhinitis. Shields showed that the effect produced by ionization is due to the impregnation of the mucous membrane with zinc in ionic form. In four patients with hay fever, ionization with sodium chloride instead of zinc solution was instituted. No improvement in the patient's symptoms followed this procedure.

The principle of ionization as used in the nose but with modifications of the technic has also been employed in the treatment of various conditions of the conjunctiva and lids. Erlanger[24] reports his results with this procedure, stating that the ionization makes the drugs more effective by increasing the permeability of the tissues. Such conditions as follicular conjunctivitis, catarrhal ulcers of the cornea, ulcerative keratitis, trachomatous keratitis, episcleritis and scleritis were treated with very satisfactory results. Various electrolites, such as zinc sulphate, calcium chloride, quinine hydrochloride, histamine and acetylcholine were used.

The effect of intranasal phenol application was studied by Vistreich[25] in 28 consecutive cases of early and late hay fever. The technic of this procedure was described in detail. It was stated that the treatment was not followed by stormy reactions or long convalescence. The results were reported as follows: 90 to 100 per cent relief was obtained in 72 per cent of the cases; 75 to 90 per cent relief in 8.3 per cent; 50 to 75 per cent relief in 12.5 per cent of the cases; and no relief in 4.2 per cent. By means of intranasal swab tests with serial dilutions of pollen extracts, it was noted that the treatment produced an actual decrease in the sensitivity of the nasal mucosa to pollen. By periodic testing it was found that this state of relative insensitiveness is not permanent. The average duration observed in this group of cases was approximately seven to eight weeks. This form of treatment was recommended as a palliative procedure in patients with hay fever presenting for treatment during the season; also in patients who previously had had unsatisfactory results from allergic treatment. It was also recommended for those patients who do not tolerate well the hypodermic injections of pollen extracts.

The surgical indications in disease of the nasal sinuses due to allergy were discussed by Mullin,[26] and several illustrative cases were presented. His observations were based on a study of 216 patients. In this group it was noted that operations had been performed previously in 52 instances with no relief of symptoms, and no studies to determine the presence of allergy had been made. Mullin found it necessary to perform the same operations after an allergic condition was diagnosed and eliminated in only 16 instances. It is obvious that if operation had yielded relief, these patients would not have sought further treatment. In this group of patients, therefore, careful studies to determine allergic sensitivity might have eliminated more than two-thirds of the nasal operations to which they were subjected. According to Mullin's experience, allergy is a complication affecting between 30 and 35 per cent of the cases of chronic disease of the nasal sinuses. These observations of Mullin emphasize the importance of primary allergic studies in these patients and the necessity of conservative

surgical procedures. The report is very instructive and should be read by everyone interested.

In a group of 13 cases of asthma subjected to pansinus operations, DeStio[27] reports that the asthma was cured in only three, or 23 per cent. The condition of three other patients was definitely improved; although the asthma was still present. The remaining seven, or 54 per cent, showed absolutely no improvement; in fact, the asthma in a few was worse after the operation. The three patients free of asthma have been well for four years. The remaining patients have also been under observation for four years since the operation. A complete frontal ethmosphenoidectomy with the Caldwell-Luc operation was done on both sides in every instance. All contents and mucous membrane of the sinuses together with all removable diseased bone were meticulously removed; yet DeStio does not believe that one could call the final result successful as far as the asthma is concerned. The patients whose asthma was relieved were predominantly those who had recently acquired asthma and sinus disease; whereas those whose conditions were unimproved had involvement of long duration.

From these observations DeStio concludes that chronic hyperplastic pansinusitis is fundamentally caused by decreased resistance to bacterial invasion as a result of the presence of an allergic or sensitizing reaction of the mucous membrane of the sinuses which is one phase of the general allergic constitution of the patient. He further believes that chronic hyperplastic pansinusitis is not the cause of asthma but that in a large majority of instances both are probably the result of the patient's allergic nature. Conservative intranasal operations in advanced chronic hyperplastic pansinusitis do not completely remove the sinus disease, although they may temporarily relieve the patient's symptoms of both sinusitis and asthma. DeStio finally states that if one is to hope for any considerable relief of asthma by the elimination of sinus infection, one must not delay until the sinus disease has reached its advanced stage.

In a group of 500 asthmatic patients, Weille[28] found sinusitis in 362, of which 223 patients had nasal symptoms which were noted almost equally in intrinsic and extrinsic asthma. Sinusitis was slightly more common in the intrinsic group. Polyps were found in 211; deviated septums in 92; severe chronic tonsils in 35; and abscessed teeth in 84. Sinus operations were performed on 100 patients, of which 17 were intranasal antrum operations, 41 radical antrum, 30 intranasal ethmoids, 5 external ethmoids, and 17 sphenoids and external frontals. More or less improvement in the asthma was noted in 66 per cent of those having sinus operation. Improvement was the same in both intrinsic and extrinsic asthma. The higher percentage of improvement in asthma followed conservative nasal surgery rather

than very drastic operations. Among 186 patients with chronic tonsillitis, 35 had tonsillectomies, and in 25 there was improvement in the asthma. Of 84 patients with abscessed teeth, 59 had the abscessed teeth extracted, and 39 of these patients had improvement of their asthma. Among 36 patients subjected to bronchoscopy as part of the treatment, 12 were improved and 3 were cured. There were 290 patients who had no surgical treatment whatever in spite of the fact that many had sinusitis, chronic tonsillitis, or abscessed teeth. The proportion of good results in this group treated only medically was about the same as that in the group treated surgically.

Riegele[29] reports favorable results in the treatment of vasomotor rhinitis by the intracutaneous injection of a mixture of cresol free from protein. Wheals were induced at two-day intervals until from six to eight were made. This form of nonspecific shock therapy was effective in some instances in which other measures had failed.

Griebel[30] reports satisfactory results in uncomplicated cases of vasomotor rhinitis by treatment with spleen extract. With the improvement of symptoms there was a disappearance of blood eosinophilia. In chronic cases of hay fever and of bronchial asthma with no eosinophilia, it was possible to produce it by means of subcutaneous injections of spleen extract although a reduction of symptoms occurred. It is believed that spleen extract exerts a regulating influence on the eosinophilo-poiesis of the bone marrow.

In the more recent rhinologic literature, a number of reports have been presented on the local immunization of the nasal mucosa with varying results. Kracaw[31] suggests that failures resulting from vaccine treatment are the result of the alterations of the bacterial antigenic complexes in the process of preparation of the vaccines. His observations were based upon the principles of vaccine preparation previously reported by Krueger by which the major antigenic substances of the bacteria are preserved in such a way as to prevent deterioration. The technic of preparing these bacterial antigens was outlined. Kracaw suggested the use of local and also general immunization in cases of allergic rhinitis of probable bacterial origin. He also advocated their use in chronic ethmoiditis, chronic sphenoiditis, and also in cases of chronic infection of the frontal sinuses.

In a previously reported series of 45 cases a year or more after completion of treatment, it was found that 28 of the 30 patients considered cured had maintained that status and of 13 patients classified as presenting satisfactory clinical improvement all remained in this category. A second group comprising 62 patients showed 52 markedly improved or cured, 2 failures, and 8 patients in whom improvement was only moderate. It was finally concluded that topical and general immunization with undenatured bacterial antigens prepared accord-

ing to the technic outlined is the method of choice for the treatment of chronic sinusitis.

The clinical studies of Goldman[32] illustrate the beneficial effect of moccasin snake venom in the treatment of recurrent epistaxis. Forty-two patients with recurrent epistaxis without any form of blood dyscrasia were treated with subcutaneous injections of moccasin snake venom. The patients were grouped according to the source of bleeding as follows: (1) telangiectasia of the nasal septum, (2) ulcerations of the nasal septum, (3) bleeding without a visible source, and (4) hemangioma of the nasal septum. No other adjuvant treatment was given. The venom therapy was effective in practically all instances either in completely arresting and controlling the nasal bleeding or in markedly diminishing its amount and frequency.

ALLERGY AND OPHTHALMOLOGY

Goodman[33] has made a very extensive study of hypersensitivity to lens protein in a group of 700 unselected patients with cataract who were admitted to the Wills Hospital during 1932. Approximately 5 per cent of the 700 patients tested intracutaneously with bovine lens antigen were found to show reactions of two-plus or greater and were regarded as being truly hypersensitive to lens protein. He believes that hypersensitivity to lens protein is acquired and is not congenital. Cataractous cortical material forms the principal antigenic factor. Hypersensitivity to lens protein occurs only in patients with diseases of the lens. No relationship was found between diabetes, syphilis, or asthmatic and hay fever allergic states and the production of autosensitization to lens protein. Attention is called to the fact that when lens material is left in the eye of a non-sensitive individual, it is not so great a source of danger as it is when left in the eye of a sensitive patient. It was also noted that the amount of lens material remaining in the anterior chamber after operation is, in general, in direct ratio to the degree of postoperative reaction whether in sensitive or in non-sensitive individuals. It is also stated that lens material left in the eye following operation may have a deleterious action because of its toxic mechanical or anaphylactic properties, the latter being productive of the severest types of reactions. A combination of the above three modes of action is also to be taken into consideration. Desensitization to lens protein is advocated before operation in hypersensitive individuals. Desensitization during the active stage of endophthalmitis phaco-anaphylactica is not considered advisable. Goodman advocates the attempt at intracapsular extraction in all favorable cases when there is any reaction to the cutaneous test with lens protein. In the event of a rupture of the capsule, thorough irrigation of the anterior chamber to remove all cortical material should be carried out.

Skin sensitivity to lens and its relation to endophthalmitis phacoanaphylactica has been discussed by Burky,[34] who advanced supportive evidence on the basis of animal experiments employing as sensitizers a combination of lens extract and of staphylococcus toxin.

Woods[35] discusses the possibility that sympathetic ophthalmia may be due to a sensitivity to the melanotic pigment of the eye and seeks to support this hypothesis through the evidence of skin reactions to tests with uveal pigment.

That allergic reactions may occur in the retina has been demonstrated by Bedell.[36] In one of his case reports, the following description was given: the entire retina was edematous and overspread with superficial striae and somewhat deeper surrounding hemorrhages. The veins were distended but not overtortuous and in places partially hidden by the overlying retina. The lumen of the arteries was irregular. The macula was clearly outlined, irregular, dark, oval, surrounded by deep retinal hemorrhages—a shower of petechial hemorrhages. After a period of about two and one-half months, these hemorrhages all disappeared. Another case was described in which the allergic reactions in the retina occurred following the injection of tetanus antitoxin. The nerve head was completely obscured by thick, white, edematous swellings which appeared like irregular balloons of various sizes and prominence with several superficial hemorrhages over them. Although the arteries were normal, the veins were at least twice their normal size.

In a paper on the clinical manifestations of allergy in the eyes, Bedell[37] calls attention to the various ocular conditions which are classified in this group. Particular attention is called to the allergic involvement of the conjunctiva, lids, and cornea. The occurrence of retinal allergy which had previously been reported by Bedell was also discussed. In the discussion of this paper Berens presented statistical data on the results obtained from intravenous injection of crude and purified cultures of various organisms from 21 patients with eye lesions and 14 patients without eye lesions. Among 103 patients with cataract on whom skin tests were done with lens protein, he found 51 negative reactions, 13 doubtful and 39 positive. The results of tests with uveal pigment in a variety of ocular conditions showed, in 82 cases, 9 positive reactions, 59 negative and 14 doubtful.

In 292 cases of external eye conditions in children (60 phlyctenular keratitis, 67 chronic conjunctivitis, 81 blepharitis, 48 trachoma, and 36 interstitial keratitis) tested by the prick method for a series of allergens by Sorsby and Benham,[38] negative results were obtained in all but one case. This patient, who had chronic conjunctivitis, gave a mild reaction to grass pollen.

A case of chronic conjunctivitis caused by hypersensitiveness to silk was reported by Taub.[39] Removal of contact to silk and specific desensitization resulted in a cure. The importance of recognizing hypersensitiveness in many cases of chronic conjunctivitis is emphasized in order to avoid more serious complications.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., CHICAGO

On the Possibility of Autumnal Hay Fever in Denmark With Report of a Case. Kragh, J.: Ugesk. f. laeger **98**: 294, 1936.

Some of the plants causing autumnal hay fever in the United States have found their way into Denmark through imported grass seed. The author says that *Ambrosia psilostachya* (Western ragweed) has gained entrance there through imported chicken feed. Because it is a hardy variety it is feared that it will become in time one of the more common weeds. A case of autumnal hay fever occurring in Denmark is discussed in detail. The patient had apparently acquired a sensitivity to these pollens while in America.

The Effect of Sympathectomy on the Sensitivity to Adrenalin of the Bronchioles. Cotui, A., Burstein, C. L., and Wright, A. M.: J. Pharmacol. & Exper. Therap. **58**: 33, 1936.

Unilateral stellate ganglionectomy was done in cats, and the animals were killed between nine and fourteen days after the operation. The lungs and part of the trachea were removed, and perfusion experiments were made comparing the operated and the unoperated sides. The perfusion rate through the excised lung on the operated side showed a marked increase after adrenalin administration over the lung on the unoperated side. This phenomenon is interpreted as due to increased sensitivity of the bronchioles on the operated side to adrenalin, resulting in a more marked bronchodilatation.

The Rôle of Microbic Organisms in Asthma. Indications for Vaccinotherapy. Vallery-Radot, P., Blamoutier, P., and Nitti, F.: Presse méd. **44**: 449, 1936.

Vaccinotherapy cannot be recommended for all types of asthma. In dry asthma it is not successful. It should be used only in cases of asthma showing symptoms of bronchitis. In these it has a favorable effect on the bronchitis, which is most remarkable as the latter, in such cases, is most resistant to other forms of treatment. The vaccine should be applied intradermally and over a prolonged period.

Some asthmatic persons show marked improvement after two or three months of treatment so that further injections seem superfluous. Others suffer rapid relapse on cessation of treatment, indicating the necessity of prolonging its application. In such cases treatment may be continued over a year with weekly injections, followed by injections every fifteen days, etc. This method gives very good results in stubborn cases, and finally there is no relapse on cessation of treatment. The best site for injection is in the back, varying the site at each injection. The initial dose of vaccine is 0.1 c.c., increased by 0.1 c.c. at each injection up to 1.5 c.c. or 2 c.c., according to the degree of local reaction. To begin with, 3 injections are given a week. When a dose of 1 c.c. is reached, the injection should be given in two places. As soon as marked improvement is noted, the number of injections weekly may be reduced to 2 and finally to 1.

Local reactions are usually slight and general reactions are not, as a rule, present, except for a slight rise in temperature some hours after the injection. In their early attempts the authors used polyvalent vaccines prepared from the organisms in the expectorate of the patient. Finally a stock vaccine was prepared containing:

	ORGANISMS PER C.C.
Hemolytic streptococci	1,250,000,000
Streptococcus viridans	1,250,000,000
Pseudomeningococci	750,000,000
Pneumococci H^3	750,000,000
Total	4,000,000,000

The use of a stock vaccine presents certain advantages, as it is often difficult to prepare an individual vaccine for each patient. Also a preventive vaccination may be given to patients suffering from increased attacks of bronchitis during certain seasons.

The predominating organisms in the expectorate of asthmatic persons are the hemolytic streptococcus and the *Streptococcus viridans*. Pseudomeningococci are also fairly common.

Other germs are less frequently encountered but may occur episodically, such as the Pfeiffer bacillus, the Friedlander bacillus, the pneumococcus, and rarely the staphylococcus.

A study of skin reactions does not support the theory of bacterial sensitization as a cause of bronchial asthma.

Radiotherapy of the Pancreas in Asthma. Delherm, L., and Stuhl, L.: Progrès méd., p. 98, 1936.

The authors treated 12 cases of asthma by irradiation of the pancreas with a result of 4 cures, 4 improvements, and 4 failures. They compare their results with those of other types of roentgen treatment, as collected from the literature. In 403 cases of asthma treated by irradiation of the chest there were 27 per cent cured, 48.4 per cent improved, and 24.6 per cent unaffected. Of 240 cases treated over the spleen 35.5 per cent were cured, 48.3 per cent improved, and 16.2 per cent were failures. The combined chest and spleen therapy gave 42 per cent cures, 37 per cent improved, and 21 per cent failures.

The mode of action of pancreas radiotherapy is discussed. Among the possible mechanisms involved are effects on the nerve endings, the vagus nuclei, and the nerve trunks. Humoral reactions and suppression of a hypersecretion of the pancreas may also be involved. The irradiation of the adjoining neurovegetative center may also be the explanation for this effect.

Results Obtained by the Use of Fever Therapy. Metz, M. H.: J. A. M. A. **106**: 1658, 1936.

The author describes three types of cases he treated successfully by fever therapy: gonorrheal ophthalmia, Sydenham's chorea, and bronchial asthma. Eight patients with severe intractable bronchial asthma were treated by means of the Kettering hypertherm. The treatments were given at weekly intervals, and the maximum number of treatments was four. All the patients were allergic, having multiple sensitivity, and had been desperate cases requiring hospitalization and frequent injections of adrenalin and morphine and oxygen administration. As a result of the fever therapy, three patients had complete relief lasting from two to six months, four had marked improvement over a period of one to twelve months, and one failed to obtain relief.

Histamine in Allergic Conditions. Dzsinich, A.: Klin. Wchnschr. **14**: 1612, 1935.

The author reviews various experimental studies tending to prove that anaphylactic shock and histamine shock are identical. The latest theory assumes that histamine is liberated by the cells of a sensitized organism and that it plays a decisive rôle in the allergic reaction. In asthma histamine is liberated from the vascular cells of the bronchi and then produces the local and general symptoms of the disease. By introducing exogenously small doses of histamine in allergic individuals they may be desensitized against the histamine formed within the organism. This idea led to the author's attempts to treat allergic conditions with small doses of histamine. His experiments included 15 cases with bronchial asthma. The choice of the proper dose for the initial injection presented great difficulties. In the first patient an overdose produced grave asthmatic attacks, worse than before treatment. To avoid these disagreeable symptoms, the author began to use very small doses for the first injection. He differentiated between the grave and the mild cases. In all cases injections were made every other day, and the first injection was intracutaneous. If no untoward reaction resulted, the same dose was injected subcutaneously after a one-day interval. The author used "Histamine sec Richter" of which 1 c.c. ampule contains 1 mg. active substance.

In the grave cases the beginning dose was 0.00001 mg. increasing by 50 to 100 per cent increments until 0.01 mg. was reached about the thirteenth treatment. In the mild cases the initial dose was 0.0001 mg., reaching the 0.01 mg. dose about the tenth treatment. In either type the 0.01 mg. dose was the maximum dose used thereafter.

In 12 cases out of 15, complete cure was achieved. During treatment the asthmatic attacks and the dyspnea disappeared. Then followed an improvement in the subjective condition. After treatment the patients gained weight and had their working capacity restored. During fifteen months since the beginning of treatment they have been entirely free of symptoms.

Three cases proved refractory to histamine treatment. Possibly they might have yielded to repeated attempts, but when 20 or more injections brought no results treatments were stopped.

Individual differences called for variations in technic. In some cases a rapid increase in the dose was possible, in others a slower procedure was necessary. Larger doses than 0.01 mg. are never advisable. The treatments were arranged in series, and often 10 to 12 injections were sufficient to stop all symptoms, while in other cases 18 to 20 injections were needed.

Roentgen Picture of the Lungs in Bronchial Asthma. Dillon, J. G., and Gureurtsch, J. B.: Fortschr. a. d. Geb. d. Röntgenstrahlen **53**: 66, 1936.

A study of 147 patients with bronchial asthma showed no roentgen findings characteristic of the condition. Tuberculous changes were found to be no more common than in any other groups. Pulmonary emphysema was found to be present in a large number of the cases and was more common the greater the duration of the asthma. Other pathologic conditions, such as bronchial glandular swellings, pleural and bronchial changes, were not more common in bronchial asthma than in other diseases.

The Effect of Intranasal Phenol Application in Hay Fever. Quantitatively Studied by a New Intranasal Swab Test With Pollen Extracts. Vistreich, F.: Laryngoscope **46**: 717, 1936.

In 24 consecutive cases of early and late hay fever the author applied pure phenol intranasally. In 75 per cent practically complete relief was obtained. In another 20 per cent the results were fair or good; only one patient failed to

obtain some degree of benefit. The reaction following such treatment lasts two or three days and consists of nasal obstruction and sometimes slight malaise. Special care must be used to prevent the phenol from dripping into the nasopharynx or on the skin of the upper lip. Two weeks, five weeks, eight weeks, and eleven weeks after treatment intranasal swab tests were made with serial dilutions of pollen extracts and compared to the tests made prior to treatment. The concentrations of extracts used for these tests were 1:100,000; 1:10,000, 1:1,000, and 1:200. It was found that the phenol treatment produced an actual decrease in the sensitivity of the nasal mucosa to pollen. The average duration of this decreased sensitiveness was found to be approximately seven to eight weeks.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY

Intravenous Testing in Postarsphenamine Dermatitis. Robinson, M.: Southern M. J. **29**: 411, 1936.

Robinson sought to determine whether resumption of arsphenamine treatment is possible in patients hypersensitive to the drug. Intradermal tests were found not reliable. Experiments with patch tests indicated that only a strongly positive test in patients who have recovered from postarsphenamine dermatitis is conclusive contraindication of further arsphenamine therapy. A negative result does not rule out arsphenamine sensitization.

An intravenous test proved more reliable; 110 patients were investigated. Many patients were tested more than once; and 11 who gave a positive intravenous test at first, later did not react, and arsenical treatment could be resumed.

The intravenous test is to be made after a three-month lapse from the date of complete healing or involution of the postarsphenamine dermatitis. Intravenous testing is carried out with those preparations causing negative or partially positive patch test, but with a different arsphenamine from the one which caused the dermatitis. The initial intravenous dose is 0.025 gm. arsphenamine, neoarsphenamine or silver arsphenamine, and 0.005 gm. mapharsen. If appreciable itching occurs, the tests go no further. Otherwise, injections are continued with careful increase of the dose until a therapeutic dose is reached.

Dermatosis as Defense Reaction in Intoxications. Gougerot, H.: Deliber. Congr. Dermat. Internat. **1**: 52, 1935.

Gougerot has been studying (since 1910) the rôle of the skin in defending the organism, under both normal and pathologic conditions. Toxic substances deposited on the skin cause extremely diverse lesions which, except for caustic destruction, are defense reactions. Internal autointoxications—of digestive, renal, hepatic origin—which cause cautaneous reactions are numerous, with or without allergy. A double defense takes place in these skin reactions: (1) the elimination effort of the skin, in order to disembarrass the organism; (2) the inflammatory destructive cutaneous reaction and dilution with edema, to decrease the harmful effect of the poisons undergoing elimination.

Pathogenetically, eczema "is a general and cutaneous defense reaction, particularly epidermal (but also affecting the cutis and even the hypoderma); often, but not constantly, following the anaphylactic mode of sensitization, and taking the aspect of eczema on account of a special porosity of the skin."

Gougerot believes that looking at eczema as a defense reaction is the best approach and guide to research.

The Factor of Immunity (Serologic) in Furunculosis. Smith, J. Ferguson: Brit. J. Dermat. **48**: 34, 1936.

Smith is convinced that the serologic factor is of slight importance. His first observations showed that hemolytic staphylococci were present in only 13 per cent of 70 persons, disproving that boils are due to a lowering of the patient's resistance. A higher titer was found in 100 patients suffering from staphylococcic infections than in the controls. In the infected group, the point of lysis was one tube farther to the right. In the third test, 20 patients were treated with formol toxoid: 10 were cured, 4 improved, 5 showed no improvement, and 1 cleared but relapsed when local treatment was discontinued. Of 36 patients receiving local treatment only, 33 were cured and 3 were unimproved.

Toxoid raises the antistaphylolysin content of the serum to about 16 times the original titer, but clinically shows no advantage over local treatment in the management of recurrent furunculosis.

Urticaria Without Urticarial Symptoms. Chevallier, Paul: Ann. de dermat. et syph. **7**: 113, 1936.

Chevallier describes two clinical forms of urticaria: (1) the usual type; (2) massive edema of the subcutaneous tissues, i.e., acute angioneurotic edema.

Urticaria may be due to some local irritation, or to an internal cause. Urticaria applies both to symptoms and to a disease complex. Pure erythematous forms are rare. Paroxysms of pruritus may occur without lesions: true "urticaria without urticaria." A mild pruritus often comes and goes in the course of chronic urticaria.

The author reports a case with severe itching over the patient's whole body but no cutaneous lesions; however, a gastroscopic examination revealed urticarial papules in the upper portion of the lesser curvature of the stomach.

Urticarial swellings can occur wherever loose connective tissue exists. A number of conditions, i.e., migraine, epilepsy, have been explained on the basis of angioneurotic edema involving the nervous system. Pulmonary edema or paroxysmal tachycardia due to involvement of the heart are examples of visceral urticaria. Cases have been reported in which cutaneous lesions were associated with gastric disturbances. Gastroscopic examination revealed marked edema of the pyloric region. In other cases without gastric symptoms, systematic gastroscopic examinations demonstrated intense swelling of the mucosa.

Urticaria has previously been considered a disease of the skin. Actually, it is a systemic disease which frequently has cutaneous manifestations.

Experimental Studies on the Specific Effect of Myceto-Allergen (Trichophytin) and of Killed Dermatophytes on Inoculated Guinea Pigs. Meriin, J. A.: Acta dermat.-venereol. **16**: 485, 1935.

Meriin reports results of his studies on guinea pigs with trichophytin. In view of the many contradictory reports in the literature on the diagnostic value of trichophytin as an allergen and the specificity of its action, Meriin exercised extreme care in the preparation of a number of strains of dermatophytes and in dilution of the various allergens. Control animals were used to find the dilution ("working dose") for each antigen, which caused no reaction in the control animals. The author concludes that the allergic trichophytin reaction in infected animals depends on: (1) the allergen used; (2) the individual peculiarities of the animal organism; and (3) the type and strain of mycetes causing the infection. The allergic reaction does not always correspond to the severity of the infection.

All myceto-allergens have two components: (1) the specific, which depends on the type of mycetes used and the method of preparation of the allergen; and (2) the nonspecific, apparently not due to the bouillon alone, but also depending on the length of time permitted for growth. Previous titration of each allergen on sound animals results in a decrease in nonspecific reactions.

The myceto-allergen is inferior to tuberculin, in that it usually causes no focal reaction; but a positive reaction is obtained in diseased animals and none in sound ones, thus demonstrating the specificity. The allergic condition of reinfected animals can be determined more readily by this method than by reinoculation.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

The Inheritance of Allergic Disease. Wiener, A. S., Zieve, I., and Fries, J. H.: Ann. Eugenics 7: 141, 1936.

From an analysis of 66 complete families including 250 children, the authors present for consideration a new theory of heredity in allergic diseases. They believe that allergy is transmitted by means of a single pair of allelomorphic genes H and h, where H determines nonallergy and h allergy. Three different genotypes are possible: genotype HH, pure normal; genotype hh, pure allergic, in which cases symptoms start before puberty; and genotype Hh, represented by individuals who usually appear normal throughout life but who transmit the abnormal gene h. When symptoms do appear in the latter genotype, they develop after puberty.

The existence of two kinds of allergic individuals is suggested by their bimodal distribution when classified according to age of onset. The authors find support for their hypothesis not only in the analysis of the family histories in their own series, but also in the published data of other investigators of this problem. They are at a loss to explain, however, the excess of males over females among allergic patients before puberty. Many tables and figures are included in the article.

On the Linkage Relations of the Genes for Allergic Disease and Genes Determining the Blood Groups MN Types and Eye Colour in Man. Zieve, I., Wiener, A. S., and Fries, J. H.: Ann. Eugenics 7: 163, 1936.

The authors studied the same family groups analyzed in the preceding communication, seeking to determine whether the genes for allergic disease were linked to those determining the four blood groups, the MN types, and the eye color.

No evidence could be found to suggest that any linkage existed between the genes determining these traits. Protocols and tables were presented analyzing in detail the results obtained in 66 families.

Vitamin C and Anaphylactic Shock in Guinea Pigs. Solomonica, B.: J. Immunol. 31: 209, 1936.

In a previous communication the author had shown that administration of anterior pituitary extract prior to sensitization was more effective in preventing anaphylactic shock than when it was given after the animal had been sensitized. Similar results were obtained with pregnancy urine extract and ovarian hormone.

In the present study the author repeated his experiments using vitamin C instead of the glandular substances. Guinea pigs were given daily subcutaneous doses of 1 to 10 mg. ascorbic acid for varying periods, the earliest starting three

weeks prior to sensitization and the latest a few hours prior to the shocking dose. Horse serum was the antigen employed, and the amount used was well above the minimum lethal shocking dose. The protective influence of vitamin C against anaphylactic shock was definite when administration preceded sensitization. Its effects were prolonged so that even when the administration of vitamin C was stopped during the period of sensitization, it tended to prevent shock. Results were most pronounced when the dosage preceded sensitization and was continued through it. Where treatment was given only while sensitization was being induced, the protective results were less regularly obtained, and much larger dosage was needed.

Active Immunization to Scarlet Fever by the Intracutaneous Method. Robinson, J. H.: J. Immunol. **31**: 373, 1936.

Twenty-four subjects were treated with scarlatinal toxin by the intracutaneous route. Ages varied from two to thirty-nine years, the average age being twenty-one years. Fifteen subjects received 5 graduated doses, five days apart, containing 50, 200, 800, 2,500, and 7,200 skin test doses of toxin, respectively. The first four doses were each contained in 0.1 c.c. of solution, the fifth in 0.288 c.c. Five subjects were treated with 50, 200, 800, 2,500, and 3,600 skin test doses, respectively. Four received 50, 200, 800, 2,500, 3,600, and 3,600 skin test doses, respectively.

Two weeks after the last immunizing dose, retests were made with one and two skin test doses. All retests resulted negatively. No systematic reactions were observed. Local cutaneous reactions averaging two inches in diameter resulted from the immunizing doses. In each case desquamation followed at the site of the latter reactions. The total amount of toxin skin test doses injected was approximately one-twelfth of the number ordinarily injected by the subcutaneous route. The longest period of observation in the above series of cases was six months.

Studies on the Sensitization of Animals With Simple Chemical Compounds. III. Anaphylaxis Induced by Arsphenamine. Landsteiner, K., and Jacobs, J.: J. Exper. Med. **64**: 717, 1936.

In previous experiments, the authors had been regularly successful in inducing specific cutaneous hypersensitiveness in guinea pigs by single intracutaneous injections of arsphenamine and neoarsphenamine. In the present study, they succeeded in demonstrating anaphylaxis in guinea pigs with these substances. Two intracutaneous injections of arsphenamine, not neutralized, were given a month apart, and after three weeks the animals were tested intravenously with a mixture of arsphenamine and normal guinea pig serum. If death did not result from the first injection, they were tested again after three weeks. About half of the 25 animals sensitized died from the first or second intravenous injection, and many others presented distinct symptoms of anaphylaxis. Of 50 controls injected intravenously with the same materials, 35 showed no symptoms, 13 coughed slightly, and 2 were slightly ill.

Another group of 7 animals, sensitized in the above manner, were given intravenous injections of the arsphenamine which had been neither neutralized nor mixed with guinea pig serum. After the first or second intravenous injection, 3 animals died of anaphylactic shock, and another showed moderate symptoms. None of the 7 controls tested in this manner showed any symptoms. Autopsies of the killed animals revealed the typical lung inflation of anaphylactic shock.

Passive Anaphylaxis Following the Immediate Injection of Antigen After Antiserum. Dean, H. R., Williamson, R., and Taylor, G. L.: J. Hygiene **36**: 570, 1936.

Guinea pigs were injected intravenously with strong rabbit anti-horse serum. This was followed within five to sixty seconds by an injection of horse serum. Of 70 animals so treated, 38 died in anaphylactic shock. Most of the remainder showed some signs of illness. Of 56 controls injected with the antiserum only 8 died. In 5 of the latter animals the serum of one rabbit which seemed to possess some unusual toxic property has been employed.

In one group of animals there were no deaths among 35 controls injected with the antiserum. Among 44 guinea pigs receiving both antiserum and antigen there were 12 early deaths and 10 late deaths. Early deaths usually occurred during the first five minutes but occasionally were delayed as long as twelve minutes. Autopsy findings in early deaths were typical of acute anaphylactic shock in the guinea pig. In late deaths there were symptoms of congestion in the abdominal organs. These findings were absent among the deaths in the controls.

When an interval of twenty-four hours was allowed to elapse between the injection of antiserum and of antigen, anaphylactic death occurred in all of the 33 animals tested.

In all the above experiments larger doses of antiserum and antigen were employed than are ordinarily needed in routine anaphylactic experiments. In most instances, the volume of horse serum employed for shocking was twice the optimal volume required for particulation with the volume of antiserum used.

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Results of Tonsillectomy in Allergic Patients: Follow-Up Study of 433 Cases. Waldbott, G., Ascher, M. A., and Giese, F. W.: Michigan State M. Soc. J. **35**: 369, 1936.

In a group of 1,112 patients with hay fever and asthma studied by Waldbott and his associates, tonsillectomy was performed in 228 before the onset of allergic symptoms and in 205 after allergic manifestations had developed. In the latter group, definite relief occurred in 1.9 per cent, temporary relief in 1.9 per cent, and aggravation of allergic symptoms occurred in 11.6 per cent. In a control group of 60 patients subjected to tonsillectomy after they had been under observation, the results were about the same. When tonsillectomy was performed for conditions other than allergy, it was successful in 35.2 per cent of the allergic group and in 36.4 per cent of the pre-allergic group as compared with 72 per cent improvement recorded in normal controls (Kaiser). Among 228 patients subjected to tonsillectomy before the onset of allergic symptoms, 14.4 per cent developed allergic manifestations within three months, 29.3 per cent within six months, and 48.6 per cent within two years after the operation. This compares with 26 per cent showing frankly allergic symptoms within three months; 47 per cent within six months, and 63 per cent within two years. In the patients whose tonsils were removed for the relief of nasal colds and bronchitis, tonsillectomy was of more benefit in the earlier age groups. The operation was less successful when performed during the pollen season. Although the results of tonsillectomies were disappointing, the authors believe that tonsillectomy should be performed in patients having frequent infections. In others with allergic catarrh of the upper part of the respiratory tract which may or may not involve the tonsils, they believe that tonsillar tissue is a definite asset to the system and should be preserved.

Neosynephrin Hydrochloride in Otolaryngology. Fitzhugh, W. M., Jr.: Arch. Otolaryng. **24**: 425, 1936.

According to the investigations of Fitzhugh, neosynephrin is chemically related to epinephrine and ephedrine. He found neosynephrin hydrochloride superior to epinephrine hydrochloride and ephedrine hydrochloride as a cardiovascular stimulant. It is as good as, but not superior to, epinephrine hydrochloride in increasing the efficiency of infiltration anesthesia. It is less toxic than epinephrine hydrochloride or ephedrine hydrochloride. It produces constriction of longer duration than that produced by ephedrine hydrochloride, and there are no apparent undesired effects.

The "Common Cold" and Asthma. Bernton, H. S.: M. Ann. District of Columbia **5**: 164, 1936.

In a study of 455 consecutive allergic patients, Bernton encountered 71 who claimed that a cold was responsible for their asthmatic seizures. Twenty-seven of the patients were ten years old or under. In this connection the value of the cytologic study of the nasal and bronchial secretions should be emphasized in making an accurate diagnosis in these cases. Otherwise it is not infrequently difficult to differentiate between an allergic exacerbation and an acute infection.

The Present Status of Bronchoscopy in Bronchial Asthma. Clerf, L. H.: Ann. Int. Med. **9**: 1050, 1936.

The value of bronchoscopy in asthma and related clinical conditions was emphasized by Clerf. He believes that bronchoscopy should be given a trial in the treatment of cases of bronchial asthma that do not respond to the usual methods. He found that the best results were obtained in patients with tracheobronchitis, excessive secretions, or bronchial obstruction. He found that vaccines obtained from the bronchoscopically removed secretions were of value in bacterial asthma.

Bronchoscopy in Pulmonary Atelectasis in Children. Bruin, M., and Gerlings, P. G.: Acta Otolaryngol. **24**: 222, 1936.

Various forms of pulmonary atelectasis in children are described by Bruin and Gerlings. Attention is called to the physical and radiologic signs by which this affection can be diagnosed with more or less certainty. The desirability of early diagnosis is indicated by the fact that within a very short time irremediable changes can take place in the occluded lung field, by which the development of bronchiectasis is promoted. Therefore, the application of bronchoscopic aspiration in cases of lung collapse is indicated as soon as possible. A number of case reports are given in detail, emphasizing various points in diagnosis and treatment by bronchoscopy. It was shown that the occlusion of the bronchus by mucous plugs may produce the same effect as a foreign body in the production of atelectasis. No doubt in many cases of bronchiectasis in children, especially those with asthma, the condition may originate as a result of plugging of the bronchi with mucus which is followed by secondary infection.

Allergic Eye Diseases. Cutino, R. M.: Am. Med. **41**: 320, 1935.

Cutino discussed various allergic eye diseases, such as the conjunctivitis associated with hay fever, vernal conjunctivitis, and a few other diseases which may also be attributed to allergy, namely phlyctenular conjunctivitis, parenchymatous keratitis, sympathetic ophthalmia, endophthalmitis anaphylactica, episcleritis, iritis, ulceration of the cornea, and marginal blepharitis. The importance of food sensitization as well as contactants and inhalants is emphasized.

Miscellaneous

Allergic Sinovitis Due to Ingestion of English Walnuts. Lewin, P., and Taub, S. J.: J. A. M. A. **106**: 2144, 1926.

The authors described a patient with intermittent hydrarthrosis. There was a definite family history of allergy with asthma, hay fever, and angioneurotic edema, but the patient had none of these. For the past ten years he had had periodic attacks of swelling and pain in the joints. The offending allergen was identified on skin tests to be English walnuts. After taking half a pound of these, a typical attack occurred within seventy-two hours and lasted about two weeks.

One-tenth cubic centimeter of the patient's serum was injected into his skin. Two hours after taking English walnuts a positive reaction occurred at that site. This was followed within three days by a typical attack which lasted about six days.

Medical Aspects of Periodontoclasia and Gingivitis. Healy, J. C., Daley, F. H., and Sweet, M. H.: J. Lab. & Clin. Med. **21**: 698, 1936.

The cause of gingivitis and its end-result, periodontoclasia, were considered due to some systemic dysfunction. Blood coming from the gums was examined and compared with that taken from the lobe of the ear. The presence of eosinophiles in the gingival blood of many patients in much greater numbers than that from the ear vein led to the suspicion that in such cases the etiology of the condition may be allergic.

A routine allergic examination was undertaken in these patients. This included a family and a personal history, local eosinophilia, and skin tests to approximately 120 allergens. Eighty-three of 101 patients responded in allergic fashion. Wheat, egg, milk, and tobacco were the commonest offenders.

Exclusion of these substances, either directly or by elimination diets in the early cases, was quite effective. Where destruction of tissue had occurred, the treatment was helpful but not curative.

Case reports of gingivitis are given which indicate a definite allergic influence.